WEST Search History

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DATE: Tuesday, August 15, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ		
☐	L52	L51 and L27	14
☐	L51	L50 and L3	28
☐	L50	(vrouenraets or dongen or visser or snow or oppelaar or stewart or postmus or stigter).in.	18365
☐	L49	L48 and L27	8
☐	L48	L47 not @py>1998	8
☐	L47	L46 and L7	146
☐	L46	L42 NEAR2 e6	212
☐	L45	L42 NEAR 2 e6	0
☐	L44	L43 and L7	18
☐	L43	L42.ab.	94
☐	L42	$chlorin	972
☐	L41	L38 not @AY>1998	3
☐	L40	5051415.pn.	1
☐	L39	L38 not @PY>1999	2
☐	L38	L37 and L27	48
☐	L37	L36 and L7	52
☐	L36	$THPC	280
☐	L35	4783529.pn.	1
☐	L34	L33 and L7	11
☐	L33	L32 and L27	33
☐	L32	sinn.in.	363
☐	L31	L30 and L27	228
☐	L30	L29 not @py>1999	266
☐	L29	(424/1.49)![CCLS]	695
☐	L28	L27 and L26	51
☐	L27	cancer$ or tumor$ or neoplas$	196960
☐	L26	L25 not @ay>1998	60
☐	L25	L13 and conjugat$	129
☐	L24	L23 and L7	12

☐	L23	m-THPC	41
☐	L22	L21 not @py>1998	41
☐	L21	L13 and L6	99
☐	L20	L11 and L7	0
☐	L19	L2 and L7	0
☐	L18	L17 and $THPC	13
☐	L17	L15 and conjugat$	495
☐	L16	L15 and L9	8
☐	L15	L6 and L7	899
☐	L14	L13 and L9	7
☐	L13	L12 and L7	181
☐	L12	L3.ab.	927
☐	L11	5162519.pn.	1
☐	L10	L9 and L8	8
☐	L9	$THPB or $THPP	132
☐	L8	L7 and L6	899
☐	L7	antibod$	173240
☐	L6	L5 or L4	3075
☐	L5	(540/145)![CCLS]	611
☐	L4	(514/183 |514/410)![CCLS]	2622
☐	L3	porphyrin or chlorin or bacteriochlorin or isobacteriochlorin	12132
☐	L2	4992257.pn.	1
☐	L1	499257.pn.	1

END OF SEARCH HISTORY

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 4	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS 5	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS 6	MAY 11	KOREAPAT updates resume
NEWS 7	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS 8	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS 9	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 10	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS 11	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and and display fields
NEWS 12	JUN 28	Price changes in full-text patent databases EPFULL and PCTFULL
NEWS 13	JUl 11	CHEMSAFE reloaded and enhanced
NEWS 14	JUl 14	FSTA enhanced with Japanese patents
NEWS 15	JUl 19	Coverage of Research Disclosure reinstated in DWPI
NEWS 16	AUG 09	INSPEC enhanced with 1898-1968 archive

NEWS EXPRESS	JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:21:36 ON 15 AUG 2006

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:21:49 ON 15 AUG 2006
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 14 AUG 2006 HIGHEST RN 901253-54-1
DICTIONARY FILE UPDATES: 14 AUG 2006 HIGHEST RN 901253-54-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=> E "M-THPC"/CN 25
E1            1     M-THIOCRESOL/CN
E2            1     M-THIZONE/CN
E3            0 --> M-THPC/CN
E4            1     M-THPP/CN
E5            1     M-THYMOL/CN
E6            1     M-THYMOL, 2,2'-(P-METHOXYBENZYLIDENE)DI-/CN
E7            1     M-THYMYL TRICHLOROACETATE/CN
E8            1     M-TMI/CN
E9            1     M-TMXDI/CN
E10           1     M-TMXDU/CN
E11           1     M-TOIN/CN
E12           1     M-TOLIDINE/CN
E13           1     M-TOLIDINE, A,A,A,A',A',A'-HEXAFLUORO-/CN
E14           1     M-TOLIDINE, A,A,A,A',A',A'-HEXAFLUORO-, DITARTRATE/CN
E15           1     M-TOLIDINE, 5-NITRO-/CN
E16           1     M-TOLIDINE, 6,6'-DICHLORO-N,N'-DICINNAMYLIDENE-/CN
E17           1     M-TOLIDINE, COMPD. WITH BUOH/CN
E18           1     M-TOLIDINE, COMPD. WITH FEI2/CN
E19           1     M-TOLIDINE, N-ACETOACETYL-N'-ACETYL-/CN
E20           1     M-TOLIDINE-PYROMELLITIC DIANHYDRIDE COPOLYMER/CN
E21           1     M-TOLIL/CN
E22           1     M-TOLIL, 4,4'-DIETHOXY-/CN
E23           1     M-TOLIL, 4,4'-DIMETHOXY-/CN
E24           1     M-TOLIL, 5,5'-DIETHOXY-4,4'-DIHYDROXY-A,A'-DIMORPHOLINO-/CN
E25           1     M-TOLIL, 5,5'-DIETHOXY-4,4'-DIHYDROXY-A,A'-DIPIPERIDINO-/CN

=> E "THPC"/CN 25
E1            1     THP-ADRIAMYCIN HCL/CN
E2            1     THP-M/CN
E3            1 --> THPC/CN
E4            1     THPE/CN
E5            1     THPO/CN
E6            1     THPO PROTEIN (MOUSE STRAIN FVB/N CLONE MGC:6080 IMAGE:3593885)/CN
E7            1     THPOH/CN
E8            1     THPOH, POLYMER WITH 1,2-ETHANEDIAMINE/CN
E9            1     THPOH, POLYMER WITH 1,3-DICHLORO-2-PROPANOL AND UREA/CN
E10           1     THPOH, POLYMER WITH 1,6-HEXANEDIAMINE/CN
E11           1     THPOH, POLYMER WITH 3-BROMOPHENOL, 1,2-ETHANEDIAMINE AND
FORMALDEHYDE/CN
E12           1     THPOH, POLYMER WITH 4-BROMOPHENOL, 1,2-ETHANEDIAMINE,
FORMALDEHYDE, TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E13           1     THPOH, POLYMER WITH 4-BROMOPHENOL, 1,2-ETHANEDIAMINE,
FORMALDEHYDE, TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT),
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM HYDROXIDE AND TETRAKIS(HYDROXYMETHYL)PHOSPHONI/CN
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E14             1     THPOH, POLYMER WITH AMMONIA/CN
E15             1     THPOH, POLYMER WITH AMMONIA, 3-BROMOPHENOL AND FORMALDEHYDE/CN
E16             1     THPOH, POLYMER WITH AMMONIA, 3-BROMOPHENOL, FORMALDEHYDE,
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E17             1     THPOH, POLYMER WITH AMMONIA, FORMALDEHYDE AND PHENOL/CN
E18             1     THPOH, POLYMER WITH AMMONIA, FORMALDEHYDE, PHENOL,
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E19             1     THPOH, POLYMER WITH AMMONIUM HYDROXIDE ((NH4)(OH)),
3-BROMOPHENOL, FORMALDEHYDE, TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E20             1     THPOH, POLYMER WITH AMMONIUM HYDROXIDE ((NH4)(OH)),
FORMALDEHYDE, PHENOL, TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E21             1     THPOH, POLYMER WITH AMMONIUM HYDROXIDE, 3-BROMOPHENOL,
FORMALDEHYDE, TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E22             1     THPOH, POLYMER WITH AMMONIUM HYDROXIDE, FORMALDEHYDE, PHENOL,
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM ACETATE (SALT) AND
TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM PHOSPHATE (1:1) (SALT)/CN
E23             1     THPOH, POLYMER WITH FORMALDEHYDE, PHENOL AND
1,3,5,7-TETRAAZATRICYCLO(3.3.1.13,7)DECANE/CN
E24             1     THPOH, POLYMER WITH UREA/CN
E25             1     THPOH-NH3/CN

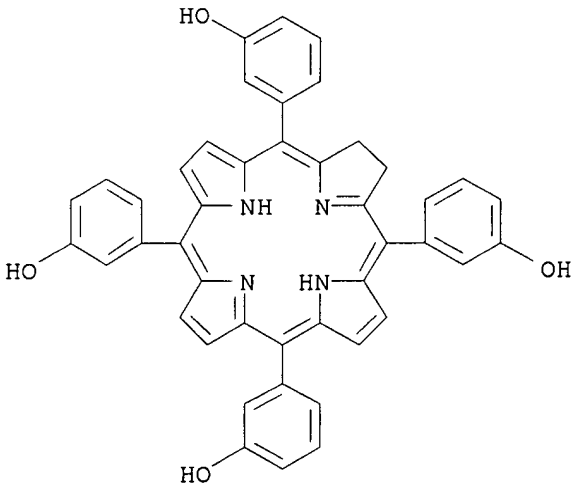
=> E "MTHPC"/CN 25
E1              1     MTHFS PROTEIN (MOUSE STRAIN MIX FVB/N, C57BL/6J CLONE MGC:37660
IMAGE:5026828)/CN
E2              1     MTHPBC/CN
E3              1 --> MTHPC/CN
E4              1     MTHSP75 (HUMAN CELL LINE HELA GENE MTHSP75)/CN
E5              2     MTI/CN
E6              1     MTI 334/CN
E7              1     MTI 446/CN
E8              1     MTI 500/CN
E9              1     MTI 501/CN
E10             1     MTI 732/CN
E11             1     MTI 790/CN
E12             1     MTI 800/CN
E13             1     MTI-II (MACROMOLECULAR-TRANSLOCATION INHIBITOR-II) (RAT LIVER)/CN
E14             1     MTIC/CN
E15             1     MTIF2 PROTEIN (HUMAN CLONE IMAGE:6150829 GENE MTIF2)/CN
E16             1     MTIF2 PROTEIN (HUMAN CLONE IMAGE:6153154 GENE MTIF2)/CN
E17             1     MTILON/CN
E18             1     MTILON T/CN
E19             1     MTILON V/CN
E20             1     MTK/CN
E21             1     MTKD 45/CN
E22             1     MTL/CN
E23             1     MTL (PASTEURELLA MULTOCIDA STRAIN IL1403 CLONE PM70 GENE MTL)/CN
E24             1     MTL 7881/CN
E25             1     MTL, POLYMER WITH
A-HYDRO-Ω-HYDROXYPOLY(OXY(METHYL-1,2-ETHANEDIYL))/CN

=> S E3
L1              1 MTHPC/CN

=> DIS L1 1 SQIDE
THE ESTIMATED COST FOR THIS REQUEST IS 6.36 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   122341-38-2  REGISTRY
```

CN Phenol, 3,3',3'',3'''-(7,8-dihydro-21H,23H-porphine-5,10,15,20-tetrayl)tetrakis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3,3',3'',3'''-(7,8-Dihydroporphyrin-5,10,15,20-tetrayl)tetraphenol
CN 5,10,15,20-Tetra(m-hydroxyphenyl)chlorin
CN 5,10,15,20-Tetrakis(m-hydroxyphenyl)chlorin
CN 8-Dihydroporphyrin-5
CN EF 9
CN Foscan
CN mTHPC
CN Temoporfin
DR 851449-56-4
MF C44 H32 N4 O4
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

296 REFERENCES IN FILE CA (1907 TO DATE)
21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
296 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.54	7.75

FILE 'CAPLUS' ENTERED AT 09:22:56 ON 15 AUG 2006
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FILE COVERS 1907 - 15 Aug 2006 VOL 145 ISS 8
FILE LAST UPDATED: 14 Aug 2006 (20060814/ED)

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http://www.cas.org/infopolicy.html

```
=> s l1
L2         296 L1

=> s antibod? or immunoconjugat?
        468285 ANTIBOD?
          2452 IMMUNOCONJUGAT?
L3      468489 ANTIBOD? OR IMMUNOCONJUGAT?

=> s l3 and l2
L4          13 L3 AND L2

=> s l2 (l) l3
L5           3 L2 (L) L3

=> d l5 ibib 1-3

L5   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2002:964122  CAPLUS
DOCUMENT NUMBER:          138:21428
TITLE:                    Photoimmunotherapies for cancer using photosensitizer
                          immunoconjugates and combination therapies
INVENTOR(S):              Hasan, Tayyaba; Savellano, Mark D.; Skobe, Mihaela
PATENT ASSIGNEE(S):       The General Hospital Corporation, USA
SOURCE:                   PCT Int. Appl., 123 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2002100326         A2    20021219    WO 2002-US13776         20020501
     WO 2002100326         A3    20031023
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
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UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2445898	AA	20021219	CA 2002-2445898	20020501
US 2002197262	A1	20021226	US 2002-137029	20020501
PRIORITY APPLN. INFO.:			US 2001-287767P P	20010501
			US 2001-338961P P	20011207
			WO 2002-US13776 W	20020501

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:747646 CAPLUS
DOCUMENT NUMBER: 135:285081
TITLE: Photodynamic therapy compounds
INVENTOR(S): Vrouenraets, Martinus Bernardus; Stigter, Marijke; Snow, Gordon Brian; Van Dongen, Augustinus Antonius Maria Silverster; Postmus, Pieter Edsge; Visser, Gerardus Wilhelmus Maria; Stewart, Fiona Anne; Oppelaar, Hugo
PATENT ASSIGNEE(S): Neth.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001074398	A1	20011011	WO 2000-GB1215	20000330

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2376001	AA	20011011	CA 2000-2376001	20000330
PRIORITY APPLN. INFO.:			WO 2000-GB1215 W	20000330

OTHER SOURCE(S): MARPAT 135:285081
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:241777 CAPLUS
DOCUMENT NUMBER: 131:41580
TITLE: Development of meta-tetrahydroxyphenylchlorin-monoclonal antibody conjugates for photoimmunotherapy
AUTHOR(S): Vrouenraets, Maarten B.; Visser, Gerard W. M.; Stewart, Fiona A.; Stigter, Marijke; Oppelaar, Hugo; Postmus, Pieter E.; Snow, Gordon B.; van Dongen, Guus A. M. S.
CORPORATE SOURCE: Departments of Otolaryngology/Head and Neck Surgery, Free University Hospital, Amsterdam, 1081 HV, Neth.
SOURCE: Cancer Research (1999), 59(7), 1505-1513
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d his

     (FILE 'HOME' ENTERED AT 09:21:36 ON 15 AUG 2006)

     FILE 'REGISTRY' ENTERED AT 09:21:49 ON 15 AUG 2006
               E "M-THPC"/CN 25
               E "THPC"/CN 25
               E "MTHPC"/CN 25
L1             1 S E3

     FILE 'CAPLUS' ENTERED AT 09:22:56 ON 15 AUG 2006
L2           296 S L1
L3        468489 S ANTIBOD? OR IMMUNOCONJUGAT?
L4            13 S L3 AND L2
L5             3 S L2 (L) L3

=> s l4 not py>1999
       7002344 PY>1999
L6             2 L4 NOT PY>1999

=> d ibib 1-2

L6   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1999:241777  CAPLUS
DOCUMENT NUMBER:          131:41580
TITLE:                    Development of meta-tetrahydroxyphenylchlorin-
                          monoclonal antibody conjugates for
                          photoimmunotherapy
AUTHOR(S):                Vrouenraets, Maarten B.; Visser, Gerard W. M.;
                          Stewart, Fiona A.; Stigter, Marijke; Oppelaar, Hugo;
                          Postmus, Pieter E.; Snow, Gordon B.; van Dongen, Guus
                          A. M. S.
CORPORATE SOURCE:         Departments of Otolaryngology/Head and Neck Surgery,
                          Free University Hospital, Amsterdam, 1081 HV, Neth.
SOURCE:                   Cancer Research (1999), 59(7), 1505-1513
                          CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER:                AACR Subscription Office
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          51    THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1998:370899  CAPLUS
DOCUMENT NUMBER:          129:133195
TITLE:                    Selective accumulation of meso-
                          tetra(hydroxyphenyl)chlorin in steroid-synthesizing
                          cells of the rat adrenal gland
AUTHOR(S):                Colombo-Benkmann, Mario; Muhm, Markus; Gahlen,
                          Johannes; Vry, Magnus-Sebastian; Deubzer, Hedwig;
                          Holloschi, Andreas; Hafner, Matthias; Heym, Christine;
                          Senninger, Norbert
CORPORATE SOURCE:         Dept. of Surgery, Univ. of Heidelberg, Heidelberg,
                          69120, Germany
SOURCE:                   Proceedings of SPIE-The International Society for
                          Optical Engineering (1998), 3260(Optical
                          Investigations of Cells in Vitro and in Vivo), 136-140
                          CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER:                SPIE-The International Society for Optical Engineering
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          15    THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
```

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> d kwic 2

L6   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
AB   . . . controls. Fluorescence was quantified on 20 μm frozen
     sections with CCD-camera and appropriate software. Immunohistochem.
     identified specific cell types with antibodies to
     steroid-synthesizing enzymes. The cortex exhibited an intense
     fluorescence, with weaker fluorescence of corticocytes in the zona
     glomerulosa compared to. . . faint mTHPC-induced fluorescence.
     Immunohistochem. revealed that intramedullary cells with intense
     fluorescence were corticocytes, showing a pos. reaction to the
     21-β-hydroxylase antibody. Peak accumulation of mTHPC was
     always observed after 24 h. Our results indicate for the first time that
     only steroid. . .
IT   122341-38-2, Phenol, 3,3',3'',3'''-(2,3-dihydro-21H,23H-porphine-
     5,10,15,20-tetrayl)tetrakis-
     RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
        (selective accumulation of meso-tetra(hydroxyphenyl)chlorin in
        steroid-synthesizing cells of rat adrenal gland)


=> file pctfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    14.86      22.61

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -0.75      -0.75

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MOST RECENT UPDATE WEEK:       200632         <200632/EW>
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    (last updated April 10, 2006) <<<

>>> NEW PRICES IN PCTFULL AS OF 01 JULY 2006. FOR DETAILS,
    PLEASE SEE HELP COST <<<

=> s mthpc or (m () thpc) or EF 9 or foscan or temoporfin
           30 MTHPC
       469445 M
           64 THPC
           22 M (W) THPC
        43233 EF
          458 EFS
        43560 EF
                (EF OR EFS)
       945640 9
           68 EF 9
                (EF(W)9)
```

```
            31 FOSCAN
             1 FOSCANS
            32 FOSCAN
                 (FOSCAN OR FOSCANS)
           264 TEMOPORFIN
L7         396 MTHPC OR (M (W) THPC) OR EF 9 OR FOSCAN OR TEMOPORFIN

=> s antibod?
L8       90279 ANTIBOD?

=> s l8 and l7
L9         304 L8 AND L7

=> s l9 not py>1999
        714367 PY>1999
L10         16 L9 NOT PY>1999

=> s conjugat? or immunoconjugat? or coupl? or link?
         77515 CONJUGAT?
          2181 IMMUNOCONJUGAT?
        340374 COUPL?
        308164 LINK?
L11     520275 CONJUGAT? OR IMMUNOCONJUGAT? OR COUPL? OR LINK?

=> s l11 and l10
L12         16 L11 AND L10

=> s photodynamic or PDT
          2126 PHOTODYNAMIC
             7 PHOTODYNAMICS
          2130 PHOTODYNAMIC
                 (PHOTODYNAMIC OR PHOTODYNAMICS)
          1532 PDT
            33 PDTS
          1549 PDT
                 (PDT OR PDTS)
L13       2910 PHOTODYNAMIC OR PDT

=> s l13 and l12
L14          8 L13 AND L12

=> d ibib 1-8

L14    ANSWER 1 OF 8     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1999040907 PCTFULL  ED 20020515
TITLE (ENGLISH):         METHODS FOR THE CONTROLLED DELIVERY OF CARBON DISULFIDE
                         FOR THE TREATMENT OF INFLAMMATORY CONDITIONS
TITLE (FRENCH):          PROCEDES D'APPORT REGULE DE DISULFURE DE CARBONE DANS
                         LE TRAITEMENT D'ETATS INFLAMMATOIRES
INVENTOR(S):             LAI, Ching-San
PATENT ASSIGNEE(S):      MEDINOX, INC.;
                         LAI, Ching-San
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 9940907            A1 19990819
DESIGNATED STATES
       W:                AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
                         ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
                         KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT
                         RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU
                         ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ
```

TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT
SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US2679 A 19990208
PRIORITY INFO.: US 1998-60/074,741 19980213

L14 ANSWER 2 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999040787 PCTFULL ED 20020515
TITLE (ENGLISH): MODIFIED PHARMACOLOGICALLY ACTIVE AGENTS AND IMPROVED THERAPEUTIC METHODS EMPLOYING SAME
TITLE (FRENCH): AGENTS MODIFIES, ACTIFS SUR LE PLAN PHARMACOLOGIQUE, ET PROCEDES THERAPEUTIQUES AMELIORES ET METTANT EN OEUVRE CES AGENTS
INVENTOR(S): LAI, Ching-San
PATENT ASSIGNEE(S): MEDINOX, INC.;
LAI, Ching-San
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9940787	A1	19990819

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US2678 A 19990208
PRIORITY INFO.: US 1998-60/074,694 19980213

L14 ANSWER 3 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999004817 PCTFULL ED 20020515
TITLE (ENGLISH): CHEMOTHERAPY SYNERGISTIC AGENT
TITLE (FRENCH): AGENT SYNERGIQUE POUR CHIMIOTHERAPIE
INVENTOR(S): WINKELMAN, James, W.;
BRIDGES, Kenneth, R.
PATENT ASSIGNEE(S): BRIGHAM & WOMEN'S HOSPITAL, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9904817	A1	19990204

DESIGNATED STATES
W: AU CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1998-US15052 A 19980722
PRIORITY INFO.: US 1997-60/053,696 19970725
US 1997-60/054,148 19970725

L14 ANSWER 4 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998055453 PCTFULL ED 20020514
TITLE (ENGLISH): CONJUGATES OF DITHIOCARBAMATES WITH PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR
TITLE (FRENCH): CONJUGUES DE DITHIOCARBAMATES COMPRENANT DES AGENTS PHARMACOLOGIQUEMENT ACTIFS ET UTILISATIONS DESDITS CONJUGUES
INVENTOR(S): LAI, Ching-San
PATENT ASSIGNEE(S): MEDINOX, INC.;
LAI, Ching-San
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9855453	A1	19981210

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US10295 A 19980519
PRIORITY INFO.: US 1997-8/869,158 19970604

L14 ANSWER 5 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998052609 PCTFULL ED 20020514
TITLE (ENGLISH): SONODYNAMIC THERAPY USING AN ULTRASOUND SENSITIZER COMPOUND
TITLE (FRENCH): THERAPIE SONODYNAMIQUE METTANT EN OEUVRE UN COMPOSE SENSIBILISANT ULTRASONORE
INVENTOR(S): ALFHEIM, Jan, Alan;
HENRICHS, Paul, Mark;
HOHENSCHUH, Eric, Paul;
JOHANNESEN, Edvin, Wilhelm;
SANDERSON, William, Anthony;
SNOW, Robert, Allen
PATENT ASSIGNEE(S): NYCOMED IMAGING AS;
ALFHEIM, Jan, Alan;
HENRICHS, Paul, Mark;
HOHENSCHUH, Eric, Paul;
JOHANNESEN, Edvin, Wilhelm;
SANDERSON, William, Anthony;
SNOW, Robert, Allen
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9852609	A1	19981126

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-GB1444 A 19980519
PRIORITY INFO.: GB 1997-9710049.9 19970519

L14 ANSWER 6 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998030242 PCTFULL ED 20020514
TITLE (ENGLISH): PHOTOCHEMOTHERAPEUTIC COMPOSITIONS
TITLE (FRENCH): COMPOSITIONS PHOTOCHIMIOTHERAPEUTIQUES
INVENTOR(S): PENG, Qian;
NESLAND, Jahn, M.;
GIERCKSKY, Karl, Erik;
MOAN, Johan;
WARLOE, Trond
PATENT ASSIGNEE(S): PHOTOCURE AS;
DZIEGLEWSKA, Hanna, Eva;
PENG, Qian;
NESLAND, Jahn, M.;

GIERCKSKY, Karl, Erik;
MOAN, Johan;
WARLOE, Trond

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9830242	A2	19980716

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-GB58 A 19980109
PRIORITY INFO.: GB 1997-9700396.6 19970110

L14 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998025648 PCTFULL ED 20020514
TITLE (ENGLISH): USE OF A TEXAPHYRIN IN OCULAR DIAGNOSIS AND THERAPY
TITLE (FRENCH): UTILISATION DE TEXAPHYRINE DANS LA PREPARATION D'UN MEDICAMENT EMPLOYE EN DIAGNOSTIC ET THERAPIE OCULAIRES
INVENTOR(S): BLUMENKRANZ, Mark, S.;
WOODBURN, Kathryn, W.;
MILLER, Richard, A.;
YOUNG, Stuart, W.
PATENT ASSIGNEE(S): PHARMACYCLICS, INC.;
BLUMENKRANZ, Mark, S.;
WOODBURN, Kathryn, W.;
MILLER, Richard, A.;
YOUNG, Stuart, W.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9825648	A2	19980618

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1997-US22661 A 19971211
PRIORITY INFO.: US 1996-08/763,451 19961211

L14 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997018805 PCTFULL ED 20020514
TITLE (ENGLISH): COMBINATIONAL THERAPEUTIC METHODS EMPLOYING NITRIC OXIDE SCAVENGERS
TITLE (FRENCH): METHODES THERAPEUTIQUES COMBINEES EMPLOYANT DES ENTRAINEURS DE MONOXYDE D'AZOTE
INVENTOR(S): LAI, Ching-San
PATENT ASSIGNEE(S): MEDINOX, INC.;
LAI, Ching-San
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE

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                         ---------------------------------
                         WO 9718805          A1 19970529
DESIGNATED STATES
      W:                 AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
                         ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT
                         LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
                         SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ
                         BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE
                         IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN
                         TD TG
APPLICATION INFO.:       WO 1996-US18124     A   19961112
PRIORITY INFO.:          US 1995-8/561,594       19951121
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=> d kwic 6

L14 ANSWER 6 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN

ABEN . . . with one or more chelating agents, and use of the same in treating disorders or abnormalities which are responsive to PDT, preferably exhibiting synergistically enhanced therapy, kits comprising same and methods of therapy and diagnosis.

DETD Photochemotherapy or photodynamic therapy (PDT) as it is also known, is a recently up-coming technique for the treatment of various abnormalities or disorders of the skin or other. . .

Psoralens are an example of directly acting photosensitizers; upon exposure to light they form adducts and cross-links between the two strands of DNA molecules, thereby inhibiting DNA synthesis. The unfortunate risk with this therapy is that unwanted mutagenic and carcinogenic. . .

Whilst such ALA esters represent a considerable advance in the field of photochemotherapy, not all abnormalities or disorders respond to PDT using known methods to prevent tumour growth and thus there is still a need for better and alternative photochemotherapeutic agents to retard or. . .

Studies conducted by the authors have shown that efficient eradication of tumours by PDT requires destruction of both cellular components and also vascular stroma of tumours (Peng & Moan, Br. J. Cancer, 72, p565-574, 1995; Peng et. . . lesions of the skin with a thickness less than 2-3 mm. No good clinical results have been obtained using topically or systemically administered ALA-PDT on thicker skin lesions or thicker lesions of the aerodigestive tract or other internal hollow organs.

However, it has now surprisingly been found, that the use of a vascular stroma-localizing photosensitizer, e.g. PhotofrinO, tetra(meso-hydroxyphenyl)chlorin (m-THPC), chlorin e6, aluminium phthalocyanine di-sulfonate or aluminium phthalocyanine tetra-sulfonate in combination with a protoporphyrin precursor photochemotherapeutic agent, e.g. ALA or its methyl or butyl esters, enhances the efficiency of PDT relative to the use of one of the agents alone. A synergistic effect was observed between the vascular stroma-

localizing photosensitizer and the. . .
. . .
growth of tumours treated in this way
were found to be reduced by using ALA at a therapeutic
dose and Photofrin']) (or m-THPC) at a low
non-therapeutic
level. The reduction in growth was significantly
greater when compared to the additive effects of results
obtained using ALA at a therapeutic dose or Photofrin])
(or m-THPC) at a therapeutic dose. This suggests a
hitherto unrecognized synergistic effect between these
different types of photochemotherapeutic agents, even at
non-therapeutic doses.

The synergistic effect, even at sub-therapeutic
levels, has significant clinical implications. Firstly,
improved PDT is achieved which is not limited to
superficial skin lesions, but may also be used to treat
thick skin lesions and superficial. . .
. . .
penetration assisting agent
and optionally with one or more chelating agents. In
particular, the therapeutic efficacy of the
photochemotherapeutic agents is enhanced, ie. PDT is
enhanced relative to the use of one of the agents alone.
. . .
such as PhotofrinO (Quadra Logic
Technologies Inc., Vancouver, Canada) and
Hematoporphyrin IX (HpIX);
Photosan III (Seehof Laboratorium GmbH, Seehof,
Wesselburenerkoog, Germany);
Clorins such as tetra(m-hydroxyphenyl)chlorins (m-
THPC) and their bacteriochlorins (Scotia Pharmaceuticals
Ltd, Surrey, UK), mono-L-aspartyl chlorin e6 (NPe6)
(Nippon Petrochemical Co., CA, USA), chlorin e6
(Porphyrin Products Inc.), benzoporphyrins. . .

benzoporphyrin derivative monoacid ring A, BPD-MA) and
purpurines (PDT Pharmaceuticals Inc., CA, USA)(e.g. tin-
ethyl etiopurpurin, SnET2);
phthalocyanines (e.g. zinc-(Quadra Logic
Technologies Inc., Vancouver, Canada), some aluminium-
or silicon phthalocyanines, which may be. . .
. . .
are considered to be those present in the stroma
in the 24 hours following administration. This may
however be manipulated by performing PDT at different
times post-administration of the agent such that the
agent(s) behaves appropriately as a vascular stroma or
lesion-localizing agent at the time. . .
. . .
precursor is ALA or a
precursor or derivative thereof and the vascular stroma-
localizing photosensitizer is a Hematoporphyrin
(particularly PhotofrinO), a chlorin (particularly m-
THPC or chlorin e6) or a sulphonated phthalocyanine
(particularly aluminium phthalocyanine di-sulfonate or
aluminium phthalocyanine tetra-sulfonate).

Malik et al in Proceedings of Photodynamic Therapy
of Cancer, 2078, p355-3621 1993, described in vitro
studies of the effects of ALA, on induction of
protoporphyrin biosynthesis, and subsequent killing. . .
. . .

of the invention or used according
to the invention may additionally be formulated and/or
administered with other agents, to improve the efficacy
of PDT. Thus for example, angiogenesis inhibitors
(anti-angiogenic drugs) which have been found to be
useful for treating tumours (O'Reilly et al., Nature
Medicine, 2,. . .

Invest., 96, p1815-18221 1995) may be used together with
compositions of the invention in PDT to further damage
the vascular system of the tumour. Angiogenesis
inhibitors which may be used include TNP-470 (AGM-1470,
a synthetic analogue of a. . . Chemical Industries Ltd.,
Osaka, Japan), angiostatin (Surgical Research Lab. at
Children's Hospital Medical Center of Harvard Medical
School) and integrin U,]3 antagonists (e.g. monoclonal
antibody to intefrin U,N, The Scripps Research
Institute, LaJolla, CA).

Alternatively, or additionally, immunotherapy
agents (e.g. antibodies or effectors such as macrophage
activating factor) or chemotherapy agents may be used to
improve PDT according to the invention. Administration
of these supplementary agents should be performed in
- 14 -
terms of route, concentration and formulation, according
to known methods for using these agents. These
additional agents may be administered before, after or
during PDT, depending on their function. For example,
angiogenesis inhibitors may be added 5-10 days after PDT
to prevent tumour regrowth.

Glucose has also been found to assist PDT when
applied either topically or systemically. Although not
wishing to be bound by theory, it appears that
administration of glucose results in a. . .
. . .
As mentioned above, a synergistic effect has been
observed, between the protoporphyrin precursor and the
vascular stroma-localising photochemotherapeutic agent,
whereby the efficiency of PDT is enhanced. Thus, this
enables sub-therapeutic dosages of the
photochemotherapeutic agent to be used ie. dosages
which, were the individual photochemotherapeutic agent
to be. . .
. . .
beneficial
results may be obtained using the protoporphyrin
precursor agent, preferably ALA or a derivative thereof,
at a therapeutic dose range, standard for PDT using such
a photochemotherapeutic agent solely, in conjunction
with a sub-therapeutic dose of the vascular stroma-
localising agent, preferably Photofrin
The concentration of the. . . -
preferably 5 to 20%; the concentration of the vascular
stroma-localizing photosensitizer, e.g. PhotofrinO is
conveniently in the range 0.1 to 1% or m-THPC is
conveniently in the range 0 10%, the concentration of
chelating agent is preferably in the range 1 to 20% e.g.
. . .
range of 0.01 to 10
mg/kg body weight, for example for Photofrin] preferably
0.01 to 1 mg/kg body weight (sub-therapeutic dose) or
for m-THPC preferably 0.01 to 0.2 mg/kg body weight

and
for the protoporphyrin precursor photochemotherapeutic agent in the range of 1 to 500 mg/kg,. . .
. . .
photochemotherapeutic agent, e.g. ALA or
a precursor or derivative thereof;
b) a second container containing a vascular stroma-localizing photosensitizer, e.g. Photofrin] or m-THPC; and optionally
C) at least one surface-penetrating agent contained within said first or second container or in a third container; and/or
d) one or. . .

other agents have been identified for use in PDT which absorb light of even higher wavelengths. Thus in conventional photochemotherapy, the wavelengths used do not excite PPp and hence do not obtain. . .
. . .
a graph showing the averaged results
for growth curves of WiDr human colonic carcinoma transplanted subcutaneously into nude mice given intravenous injections of m-THPC and/or
intraperitoneal
administration of ALA, followed, 3 hours later, by laser light irradiation (632 nm, 15 OMW/CM2 for 15 min). * Control (no drug, no light) ; A Control (light only) ; * ALA 250 mg/kg, irradiation after 3 hours; V m-THPC
75
pg/kg, irradiation after 3 hours; M ALA 250 mg/kg and m-THPC 75 gg/kg, irradiation after 3 hours; abscissa shows days after treatment; ordinate shows relative tumour volume. Bars indicated standard error of mean. . .

Example 2
PDT using ALA + Photofrin]
MATERIALS AND METHODS
Chemicals
5-aminolevulinic acid (ALA) hydrochloride was purchased from Sigma Chemical Company (St. Louis, MO). ALA was freshly dissolved. . .
. . .
exposure. The fluence rate of the light on
the tumor area was regularly controlled by a calibrated integrating sphere with a photodiode coupled to a digital multimeter (Keithley Instruments, Germany) before and immediately after light illumination.

PDT efficiency using ALA or Photofrin] alone, or a combination of ALA with Photofrin]
Mice with tumors of the appropriate size were divided into. . . intraperitoneal administration of 0.1 ml saline; group 2 (control-light only) the tumours were irradiated at the same doses as those for groups receiving PDT treatment; group 3 (ALA alone), mice were given an intraperitoneal injection of ALA of 250 mg/kg body weight, followed, 3 hours later,. . .
. . .
days. Laser light given to
tumors of mice receiving ALA had an effect on the tumor growth. No effect was seen after PDT with Photofrin] alone at a dose of 1 mg/kg, a dose that does not induce any skin phototoxicity (data not shown). PDT with a combination of ALA (250 mg/kg) and Photofrine (1 mg/kg)

inhibited the growth of the tumors more efficiently than did PDT using ALA (250 mg/ kg) alone.

Exam-ple 3
PDT using ALA + m-THPC
PDT was performed essentially as described in Example 2 using the following groups of animals, with at least 3 animals per group: group 1 (control), mice were given neither ALA (m-THPC) nor light, only intraperitoneal administration of 0.1 ml saline; group 2 (light only), tumors were irradiated with light at the same doses as those for groups of PDT treatment; group 3 (ALA alone), mice were given an intraperitoneal injection of ALA of 250 mg/kg body weight, followed, 3 hours later, by light exposure (632 nm) as described earlier; group 4 (m-THPC
alone), mice were given an intravenous injection of m-THPC of 75 Ag/kg body weight (a dose that does not induce any skin phototoxicity), followed, 3 hours later, by light irradiation (652 nm); group 5 (ALA and m-THPC),
mice were given an intraperitoneal injection of 250 mg/kg ALA and an intravenous injection of 75 Ag/kg m-THPC, the tumours were exposed to light (at respective wavelengths) 3 hours for both ALA and m-THPC. Responses
of the treated tumors were evaluated as described previously.
. . .
light given to tumors of mice receiving
only ALA had an effect on the tumor growth, but no effect was seen after PDT with m-THPC at a dose of 75
Ag/kg. PDT with a combination of ALA (250 mg/kg) and m-THPC (75 Ag/kg) synergistically enhanced the effect on inhibiting the tumor growth.

CLMEN 7 A pharmaceutical composition as claimed in claim 6 wherein the vascular stroma-localizing agent is Photofrin], m-THPC, chlorin e6, aluminium phthalocyanine
di-sulfonate or aluminium phthalocyanine tetra-
- 38 -
sulfonate, or a precursor or derivative thereof.

=> d kwic 7

L14 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ABEN The use of texaphyrins for ocular diagnosis and therapy is provided, especially use of
photosensitive texaphyrins for photodynamic therapy of conditions of the eye characterized by
abnormal vasculature, such as macular degeneration, or pterygium, for example. The photosensitive. . .

DETD . . . strategies have sought more selective closure of the blood vessels to
preserve the overlying neurosensory retina. One such strategy is photodynamic therapy
(PDT), a treatment technique that uses a photosensitizing dye and non-damaging light
corresponding to the sensitizer's absorption profile to produce

cytotoxic. . .

The effectiveness of PDT is predicated on three additional factors: i) The photosensitive dyes used in PDT preferably have the ability to localize at the treatment site as opposed to surrounding tissue. ii) The high reactivity and. . . a beam of intense, non-damaging, light to be delivered accurately to many parts of the body. For a review of photodynamic therapy, see U.S. patent 5,252,720 (incorporated by reference herein)

0 Photodynamic therapy of conditions in the eye characterized by neovascularization has been attempted using conventional porphyrin derivatives such as hematoporphyrin derivative. . . in U.S. Patent 5,576,013 to Williams, et 5 al. for example. In addition, phthalocyanine and benzoporphyrin derivatives have been used in photodynamic treatment. PCT publication WO 95/24930 and Miller et al., (Archives of Ophthalmology, June, 1995) relate to treatment of eye conditions. . .

4
1994, 21/6, suppl. 15 (4-10)) relates to photodynamic therapy with porfimer sodium (PHOTOFRIN&rey;, requiring light of 630 nm and causing cutaneous photosensitivity that may last for up to. . . derivative (BPD verteporfin, causing cutaneous photosensitivity of a few days). Lin et al. (IOVS 34:1303 Abstract 2953, 1993) relate to the photodynamic occlusion of choroidal vessels using benzoporphyrin derivative BPD-MA. Baumal et al. (Invest. Ophthalmol. Vis. Sci. 37/3:S122 (abstract) 1996) relates to PDT of experimental choriodal neovascularization with tin ethyl etiopurpurin (SnET2) and 665 nm irradiation. BPD and SnET2 are insoluble in aqueous. . .

Texaphyrins are aromatic pentadentate macrocyclic "expanded porphyrins" useful as MRI contrast agents, as radiosensitizers, as chemosensitizers, and in photodynamic therapy. Texaphyrin is considered as being an aromatic benzannulene containing both 187c- and 227c-electron delocalization pathways. Texaphyrin molecules absorb strongly. . .
. . .
of a texaphyrin in the preparation of a pharmaceutical composition for use in ocular diagnosis and therapy, in particular, therapy involving photodynamic therapy of conditions of the eye characterized by abnormal vasculature. Accordingly, an aspect of the invention is directed to use. . .
. . .
of ocular blood vessels due to their localization in areas of abnormal permeability or damage. Texaphyrins are particularly effective in PDT in that the wavelength of light used with texaphyrin is readily transmitted

through blood and
other endogenous pigments to effect photodynamically-mediated destruction of
pigmented and pigment-related tissue as described in USSN 08/914,272, incorporated
by reference herein. PDT requires higher levels of light than for imaging
. . .
an advantage in the ocular methods of
use provided herein, providing for rapid infusion as a bolus as compared to BPD,
mTHPC, or SnET2 which require solubilizing vehicles such as lipid environments, for
example; and further obviating the need for a lipophilic. . .
complex. Diagnostic
5 imaging and therapy can be performed with one agent by using texaphyrin as both an
angiographic and a PDT agent, thus enabling both accurate determination of dye
localization prior to treatment and immediate confirmation of photodynamic closure
following treatment
. . .
(M) Choroidal neovascularization (membrane)
FWHM - full width half maximum
HDL - high-density lipoproteins
ICG indocynanine green
LDL Low density lipoprotein
Lu(III)T2BET - lutetium texaphyrin, T2BET
mTHPC Tetra(m-hydroxyphenyl)chlorin
NZW New Zealand White
OD Right eye
OS Left eye
PDT Photodynamic therapy
SN Superonasal
SnET2 - Tin etiopurpurin
ST Superotemporal
TGF-b - Transforming growth factor-b
Txp Texaphyrin
0 VEGF Vascular endothelial growth factor
BRIEF DESCRIPTION OF THE DRAWINGS
FIG.. . .

FIG. 8. Fluorescein angiogram of the rabbit in FIG. 7 after receiving PDT using
LuT2BET. The image depicts closure of the vessels as evidenced by fluorescein
staining and retention in the PDT targeted lesion
. . .
of texaphyrins in the preparation of a
pharmaceutical composition for use in ocular diagnosis and therapy; especially
diagnostic angiograms, and photodynamic therapy of conditions of the eye
5 characterized by abnormal vasculature. "Abnormal vasculature", as used herein, means
undesirable vasculature; neovasculature; irregular,. . .

The texaphyrin or texaphyrin metal complex for use in ocular diagnosis or
photodynamic therapy may have structure I:
n
25
I

10
or may have structure II:
5
II
M is a divalent metal cation selected from the group consisting of. .
.
. . .
hydroxyalkyl, alkoxy, hydroxyalkoxy,
hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy, carboxyalkyl,
carboxyamide,
carboxyamidealkyl, amino, aminoalkyl, a site-directing molecule, a
catalytic group, or a
couple that is coupled to a site-directing molecule
or to a catalytic group
. . .
R12 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl,
hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl,
carboxyalkyl,
carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or a couple
that is coupled to a
5 saccharide, to a site-directing molecule, or to a catalytic group; and
n is an integer value
less than or. . .

Photosensitive texaphyrins are used for photodynamic therapy.
A
5 photosensitive texaphyrin may be a free-base texaphyrin or may be
metallated with a
diamagnetic metal. The term "photosensitive",. . .

Representative examples of oxyalkyls include the alkyl groups as herein
described having ether linkages. "Oxyalkyl" is meant to
include polyethers with one or
more functional groups. The number of repeating oxyalkyls within a
substituent. . .

Oxyhydroxyalkyl means alkyl groups having ether or ester
linkages, hydroxyl
groups, substituted hydroxyl groups, carboxyl groups, substituted
carboxyl groups or
the like

"Carboxyamidealkyl" means alkyl groups with secondary or tertiary amide
linkages or the like. "Carboxyalkyl" means alkyl groups having
hydroxyl groups,
carboxyl or amide substituted ethers, ester linkages, tertiary
amide linkages removed
from the ether or the like

In an embodiment of the present invention, texaphyrins are further
coupled to
site-directing molecules to form conjugates for targeted in
vivo delivery. "Site-
directing" means having specificity for targeted sites. "Specificity for
targeted sites"
means that upon contacting the texaphyrin-conjugate with the
targeted site, for example,
5 under physiological conditions of ionic strength, temperature, pH and
the like, specific
binding will occur. The interaction may occur due to specific
electrostatic,
hydrophobic, entropic or other interaction of certain residues of the
conjugate with
specific residues of the target to form a stable complex under

conditions effective to
promote the interaction. A site-directing. . . limited to:
lipoproteins including low density
lipoprotein; cholesterol; polyamides including peptides having affinity
for an ocular
receptor; proteins such as antibodies or an immunologically
active fragment thereof;
15
oligonucleotides complementary to an ocular DNA or RNA; histamine;
hormone
mimics such as morphine; a. . .
. . .
derivatives of amino acids
like; derivatives thereof; and texaphyrin metal complexes. The term
"appended to the
texaphyrin complex-site directing molecule conjugate" means
that the catalytic groups
are attached either directly to the texaphyrin metal complex or to the
texaphyrin
complex via a linker or couple of variable length,
or are attached to the ligand portion o
0 a texaphyrin complex-ligand conjugate either with or without
a linker or couple of
variable length

A preferred site-directing molecule for coupling to texaphyrin
is low density
lipoprotein (LDL). Human LDL is a physiologic serum protein metabolized
by cells
via uptake by. . . the lipoprotein phase of the blood, LDL is
expected to more efficiently
deliver texaphyrin to the target tissue. A texaphyrin-LDL
conjugate is selective for
neovascularization since leakage of the conjugate is expected
to occur only in
neovasculature due to the large size of the conjugate. LDL can
be isolated and purified
0 according to the procedure of Hauel et al., (J. Clin. Invest.,
34:1345, 1995)

A couple may be described as a linker, i.e., the
covalent product formed by
reaction of a reactive group designed to attach covalently another
molecule at a distance
16
from the texaphyrin macrocycle. Exemplary linkers or
couples are amides, amine,
disulfide, thioether, ether, ester, or phosphate covalent bonds

In most preferred embodiments, conjugates and appended groups
are covalently
bonded to the texaphyrin via a carbon-carbon, carbon-nitrogen,
carbon-sulfur, or a
carbon-oxygen bond, more preferably a. . .
. . .
for use in the present
invention, the invention is not limited thereto and any photosensitive
texaphyrin may b
0 useful for PDT, and any fluorescent texaphyrin may be useful
for angiography

TXP	R7	R8	R9	RIO
R	R12			
Al	O(CH2)30H	O(CH2)30H	H	H

```
H          H
A2          O(CH2CH2O)3CH3        O(CH2CH2O)3CH3
"
A3     O(CH2)    CON-linker-VEGF, n=1-10
fi         il
A4     O(CH2)1CON-linker-VEGF, n--l-10H                fi
Il           fi         fi
A5            OCH2CO-VEGF                              Il          il
fi
A6           O(CH2CH2O)3CH3                                        "
fi
A7        OCH2CON-linker-VEGF     O(CH2CH2O)3CH3
"
A8            OCH2CO-VEGF                                        "
"           "
A9           O(CH2CH2O),QOCH3
'l          il
A10        OCH2CON(CH2CH2OH)2           H                Il          il
Il          "
All          CH2CON(CH3)CH2_                           "           "
"
(CHOH)4CH20H
A12                ".   .   .  R1
A15                      OCH3                                OCH3
et                 il                if                "
A16                OCH2CO2-VEGF                                H
fi                 fi                                  "
A17             O(CH2)    000H, n=1-10                          if
et                 "                 "                 f
A19        YCOCH2-linker-VEGF, Y=NH,O                          et
if                 et                "                 i
A20                 O(CH2)2CH2OH                        O(CH2)2CH2OH
et                 Il                il                "
A21                        "                                    it
If                 et                il                e
A22                  OCH2000H                          O(CH2CH2O)3CH3
If                 el                il                "
A23            O(CH2).CO-VEGF, n=1-10                          H
il                 et                "
A24                O(CH2CH2O)3CH3                  O(CH2CH2O)rt
linker-                                    fi                te
"
VEGF, n=1-10
A25                      OCH3                          OCH2CO-VEGF
"
A26                                                      CHzCO-VEGF
Il                 fi                et                "
A27                                                             il
il                fi                t
A28                      OCH3                            CH2CO-VEGF
H                 H                 H                 H
A29                                                           OCH3
if                 et                le                e
A30                          If
"                  fi                "                 f
A31                         H                        O(CH2).000H, n=1-10
fi                 if                et                "
A32                                                  (CH2),-CON-linker
-VEGF,              Il                  te                 il              "
TXP                                            R7
R8                                        R9
R10                           R11                           R1
n=1-10
A33                                       OCH3
```

O(CH2CH2O)3-CH3 fi
Il "
A34 "
" " "
11
A36. . . OCH2CO- VEGF
"
A92 CH2CO- VEGF
CH2CO- VEGF
"
A93 le
Il fi
Il
"
A94 il
If fi
if fi
A95 H
YCOCH2-linker-
et If
Il "
VEGF
Y=NH,O
A96 O(CH2CH2O)3CH3
O(CH2CH2O)5-VEGF
"
A97 Il
il el
et fi
A98 H O(CH2)3CO-VEGF et Il et
"
A99 II. . .
. . .

by reference
herein could extend and refine the referenced basic synthetic chemistry to produce
texaphyrins having various substituents. For example, polyether-linked
polyhydroxylated groups, saccharide substitutions in which the saccharide is appended
via an acetal-like glycosidic linkage, an oligosaccharide or a polysaccharide may be
similarly linked to a texaphyrin. A doubly carboxylated texaphyrin in which the
carboxyl groups are linked to the texaphyrin core via aryl ethers or functionalized alkyl
substituents could be converted to various esterified products wherein the ester linkages
serve to append further hydroxyl-containing substituents. Polyhydroxylated texaphyrin
derivatives may be synthesized via the use of secondary amide linkages. Saccharide
0 moieties may be appended via amide bonds. Polyhydroxylated texaphyrin derivatives
containing branched polyhydroxyl (polyol) subunits may be appended to the texaphyrin
core via aryl ethers or ester linkages
. . .

Treatment of carboxylated texaphyrins with thionyl chloride or p-nitrophenol
acetate would generate activated acyl species suitable for attachment to monoclonal
5 antibodies or other biomolecules of interest. Standard in situ coupling methods (e.g.,

1,1'-carbonyldiimidazole) could be used to effect the conjugation

The texaphyrin to be used in the angiographie or photodynamic methods of the invention will be administered in a pharmaceutically effective amount. By "pharmaceutically effective" is meant a dose that. . .

. . .

Therefore, the dose is adjusted with respect to other parameters, for example, fluence, irradiance, duration of the light used in photodynamic therapy, and the time interval between administration of the dose and the therapeutic irradiation. Such parameters should be adjusted to. . .

. . .

a wavelength similar to the absorbance of the texaphyrin, usually either about 400-500 nm or about 700-800 Mn. In the present photodynamic therapy methods, the light source may be a laser, a light-emitting diode, or filtered light from, for example, a xenon. . .

. . .

endoplasmic reticulum, the Golgi apparatus, and the nucleus. Occlusion of the vasculature is thought to be a major mechanism of photodynamic therapy which occurs by damage to endothelial cells with subsequent platelet adhesion, degranulation, and thrombus formation

. . .

may be used when additional dyes such as fluorescein are being used in combination with the texaphyrin, a CCD camera (charge-coupled device) is preferable as being able to capture emissions at higher wavelengths. As a result, one can obtain more sophisticated. .

.

EXAMPLE

Texaphyrins for Angiography and for Photodynamic Therapy of Vascular Lesions of the Eye

The present example provides results from studies using Lu(III)T2BET, cited herein, for fluorescent digital angiography of the eye and for photodynamic therapy of vascular lesions of the eye. LuT2BET has broad absorption bands at 470 and 732 run (E=32,000 M-'cm' at 732. . .

. . .

texaphyrin fluorescence angiography appears safe. In further studies, vascular lesions including neovascularization was induced in albino rabbits (NZW) using photocoagulation. PDT using LuT2BET was carried out on the induced lesions. The results demonstrate that vascular occlusions, areas of decreased 0 perfusion, and. . . showing that texaphyrin is an effective agent for fluorescent angiography. The results also demonstrate closure of induced vascular lesions using PDT with texaphyrin, showing that texaphyrin is an effective agent for PDT of abnormal vasculature of the eye. Therefore, selective

37
accumulation of Lu(III)T2BET in areas of neovascularization should facilitate diagnosis
and photodynamic therapy of age-related macular degeneration and other disorders
related to abnormal vasculature

0 Photography. Fundus photography and fluorescence angiograms were performed with the TOPCONTM 50VT camera coupled to the Ophthalmic Imaging
System (Ophthalmic Imaging System Inc., Sacramento, CA). Lu-Tex imaging was
performed with conventional excitation and interference. . .

PDT Protocol. Animals received Lu(III)T2BET, 30 minutes post injection laser
light at 488 run, spot size of 1000 µm, was directed to. . .

Fluorescein angiography was performed throughout the procedure, from prior to until
after PDT

FIG. 7 and FIG. 8 demonstrate fluorescein angiograms of a rabbit's eye having
an induced lesion before and after receiving PDT with LuT2BET
. . .
FIG. 7 and FIG. 8 demonstrate fluorescein angiograms of a rabbit's eye having
an induced lesion before and after receiving PDT with LuT2BET. Thirty minutes after
injection with LuT2BET, laser light at 488 nm, spot size of 1000 µm, was directed to
40
the lesion via a slitlamp lens system. Prior to PDT, fluorescence fluorescein
angiography revealed some hyperfluorescence at early phases, which leaked over time
(shown in FIG. 7). After PDT, the fluorescein angiogram revealed hyperfluorescence in
the vessel (FIG. 8), indicative of reduced blood flow and therefore of vessel closure

There was limited fluorescence leakage outside of the PDT -treated vessel (compare
FIG. 7 with FIG. 8)
. . .
for angiography of the eye, especially for visualizing the retinal and choroidal
vascular systems, and as a photosensitive agent for photodynamic therapy of vascular
lesions of the eye. Lu(III)T2BET demonstrated filling of retinal and choroidal
vasculature, accumulation and fluorescence in areas of. . .

Closure of induced lesions was observed after PDT with LuT2BET. No damage
to surrounding vessels or tissues was observed. Further, no damage was observed in
control normal choroid or retinal tissue. The PDT treatment therefore demonstrated
selectivity, an advantage over techniques, such as laser photocoagulation, for example
. . .
either of the two most commonly used contrast agents, Na-

fluorescein and indocyanine green. Additionally, Lu(III)T2BET has relatively more
efficient energy-coupling capabilities than either agent. Lu(III)T2BET may be
sequentially used advantageously for both angiography and PDT following a single or
multiple administration

CLMEN. . . hydroxyalkyl, alkoxy,
hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy,
carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, a
0 site-directing molecule, a catalytic group, or a couple that is coupled to a
site-directing molecule or to a catalytic group;
R6 and R9 are independently selected from the groups of R,-R4, R7 and.
. . than iodide and the haloalkyl is other than iodoalkyl;
hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl,
carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or
a couple that is coupled to a saccharide, to a site-directing molecule, or
to a catalytic group;
0 R is alkyl, alkenyl, oxyalkyl, or hydroxyalkyl having. . .

20. Use of a photosensitive texaphyrin in the preparation of a pharmaceutical
composition for photodynamic therapy of macular degeneration of a subject
. . .
hydroxyalkyl, alkoxy,
hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy,
carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, a
site-directing molecule, a catalytic group, or a couple that is coupled to
0 site-directing molecule or to a catalytic group;
R6 and R9 are independently selected from the groups of R,-R4, R7. . .
R12 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl,
5 hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl,
carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or
a couple that is coupled to a saccharide, to a site-directing molecule, or
to a catalytic group;
R13 is alkyl, alkenyl, oxyalkyl, or hydroxyalkyl having up. . .

=> ?chlorin or ?porphyrin
?CHLORIN IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s ?chlorin or ?porphyrin
561 ?CHLORIN
4428 ?PORPHYRIN
L15 4618 ?CHLORIN OR ?PORPHYRIN

=> d his

(FILE 'HOME' ENTERED AT 09:21:36 ON 15 AUG 2006)

FILE 'REGISTRY' ENTERED AT 09:21:49 ON 15 AUG 2006
E "M-THPC"/CN 25
E "THPC"/CN 25
E "MTHPC"/CN 25

```
L1            1 S E3

     FILE 'CAPLUS' ENTERED AT 09:22:56 ON 15 AUG 2006
L2          296 S L1
L3       468489 S ANTIBOD? OR IMMUNOCONJUGAT?
L4           13 S L3 AND L2
L5            3 S L2 (L) L3
L6            2 S L4 NOT PY>1999

     FILE 'PCTFULL' ENTERED AT 09:24:55 ON 15 AUG 2006
L7          396 S MTHPC OR (M () THPC) OR EF 9 OR FOSCAN OR TEMOPORFIN
L8        90279 S ANTIBOD?
L9          304 S L8 AND L7
L10          16 S L9 NOT PY>1999
L11      520275 S CONJUGAT? OR IMMUNOCONJUGAT? OR COUPL? OR LINK?
L12          16 S L11 AND L10
L13        2910 S PHOTODYNAMIC OR PDT
L14           8 S L13 AND L12
L15        4618 S ?CHLORIN OR ?PORPHYRIN

=> s l5 and l13
'CN' IS NOT A VALID FIELD CODE
             0 MTHPC/CN
         90279 ANTIBOD?
          2181 IMMUNOCONJUGAT?
             0 L2 (L) L3
L16          0 L5 AND L13

=> s l15 and l13
L17        922 L15 AND L13

=> s l13/ab
           312 PHOTODYNAMIC/AB
           107 PDT/AB
             1 PDTS/AB
           107 PDT/AB
                 ((PDT OR PDTS)/AB)
L18        353 (PHOTODYNAMIC/AB OR PDT/AB)

=> s l18 and l15
L19        251 L18 AND L15

=> s l19 and l8
L20        124 L19 AND L8

=> s l20 and l11
L21        119 L20 AND L11

=> s l21 no py>1998
MISSING OPERATOR L21 NO
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l21 not py>1998
        781927 PY>1998
L22         33 L21 NOT PY>1998

=> s cancer? or tumor? or neoplas?
         80623 CANCER?
         67255 TUMOR?
         23370 NEOPLAS?
L23     100308 CANCER? OR TUMOR? OR NEOPLAS?

=> s l23 and l22
```

```
L24         33 L23 AND L22

=> s l15/clm
LEFT TRUNCATION IGNORED FOR FILE 'PCTFULL'
LEFT TRUNCATION IGNORED FOR FILE 'PCTFULL'
           136 CHLORIN/CLM
           667 PORPHYRIN/CLM
L25        734 (?CHLORIN/CLM OR ?PORPHYRIN/CLM)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s l24 and l25
L26         11 L24 AND L25

=> s l8/clm
L27      34879 (ANTIBOD?/CLM)

=> d his

     (FILE 'HOME' ENTERED AT 09:21:36 ON 15 AUG 2006)

     FILE 'REGISTRY' ENTERED AT 09:21:49 ON 15 AUG 2006
                E "M-THPC"/CN 25
                E "THPC"/CN 25
                E "MTHPC"/CN 25
L1            1 S E3

     FILE 'CAPLUS' ENTERED AT 09:22:56 ON 15 AUG 2006
L2          296 S L1
L3       468489 S ANTIBOD? OR IMMUNOCONJUGAT?
L4           13 S L3 AND L2
L5            3 S L2 (L) L3
L6            2 S L4 NOT PY>1999

     FILE 'PCTFULL' ENTERED AT 09:24:55 ON 15 AUG 2006
L7          396 S MTHPC OR (M () THPC) OR EF 9 OR FOSCAN OR TEMOPORFIN
L8        90279 S ANTIBOD?
L9          304 S L8 AND L7
L10          16 S L9 NOT PY>1999
L11      520275 S CONJUGAT? OR IMMUNOCONJUGAT? OR COUPL? OR LINK?
L12          16 S L11 AND L10
L13        2910 S PHOTODYNAMIC OR PDT
L14           8 S L13 AND L12
L15        4618 S ?CHLORIN OR ?PORPHYRIN
L16           0 S L5 AND L13
L17         922 S L15 AND L13
L18         353 S L13/AB
L19         251 S L18 AND L15
L20         124 S L19 AND L8
L21         119 S L20 AND L11
L22          33 S L21 NOT PY>1998
L23      100308 S CANCER? OR TUMOR? OR NEOPLAS?
L24          33 S L23 AND L22
L25         734 S L15/CLM
L26          11 S L24 AND L25
L27       34879 S L8/CLM
```

```
=> s l24 and l27
L28         10 L24 AND L27

=> s l28 and l26
L29          2 L28 AND L26

=> d ibib 1-2

L29    ANSWER 1 OF 2     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1995024930 PCTFULL  ED 20020514
TITLE (ENGLISH):         USE OF GREEN PORPHYRINS IN OCULAR DIAGNOSIS AND THERAPY
TITLE (FRENCH):          UTILISATION DE PROPHYRINES VERTES POUR LE DIAGNOSTIC ET
                         LA THERAPIE OCULAIRE
INVENTOR(S):             MILLER, Joan, W.;
                         GRAGOUDAS, Evangelos, S.
PATENT ASSIGNEE(S):      MASSACHUSETTS EYE & EAR INFIRMARY
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 9524930            A1 19950921
DESIGNATED STATES
       W:                AU CA JP KR AT BE CH DE DK ES FR GB GR IE IT LU MC NL
                         PT SE
APPLICATION INFO.:       WO 1994-US2639        A  19940314

L29    ANSWER 2 OF 2     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        1991014456 PCTFULL  ED 20020513
TITLE (ENGLISH):         IMPROVED COMPOSITIONS FOR PHOTODYNAMIC THERAPY
TITLE (FRENCH):          COMPOSITIONS DE THERAPIE PHOTODYNAMIQUE AMELIOREES
INVENTOR(S):             LIU, Daniel
PATENT ASSIGNEE(S):      QUADRA LOGIC TECHNOLOGIES INC.;
                         LIU, Daniel
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 9114456            A2 19911003
DESIGNATED STATES
       W:                AT AU BB BE BF BG BJ BR CA CF CG CH CM DE DK ES FI FR
                         GA GB GR HU IT JP KP KR LK LU MC MG ML MR MW NL NO PL
                         RO SD SE SN SU TD TG US
APPLICATION INFO.:       WO 1991-CA93          A  19910322
PRIORITY INFO.:          US 1990-498,042          19900322


=> d kwic 2

L29    ANSWER 2 OF 2     PCTFULL   COPYRIGHT 2006 Univentio on STN
ABEN   Porphyrin-type photosensitizers useful in photodynamic
       therapy can be formulated as water
       soluble drugs by conjugation of the photosensitizer to a
       hydrophilic polymer. Conjugation of the
       photosensitizer in varying ratios to the polymer, such as polyvinyl
       alcohol, provides compositions
       which are readily soluble and. . . biodistribute in a fashion equal
       to or advantageous over that obtained
       when the photosensitizer is administered alone. In addition, these
       conjugates which further contain
       a target specific component provide a mechanism for homing to the
       desired target tissue, as well as. . .
```

DETD IMPROVED COMPOSITIONS FOR PHOTODYNAMIC THERAPY

Technical Field

The invention relates to pharmaceutical compositions useful in photodynamic therapy, More specifically, the invention concerns conjugates of porphyrin-type photosensitizers with hydrophilic polymers as active ingredients in compositions which can be used to effect the destruction or impairment of suitable target moieties such as cancer cells and viruses.

Background Art

The.use of porphyrin-type photosensitizers for the selective destruction of, for example, cancer cells in animal subjects has been known for several decades. The initial work utilized a mixture of porphyrins prepar]d from hematoporphyrin by treatment of this starting material with a mixture of sulfuric and acetic acids to result in a composition known specifically as hematoporphyrin derivative (HPD). (See, for example, Porphyrin Photosensitization Kessel, D,, et al,, eds.

(1983) Plenum Press,)

HPD and related porphyrin-type photosensitizers appear to localize in malignant cells at the expense of normal tissues. The cells in which the HPD has been accumulated. . . cells in which they are localized is exerted (see, for example, Diamond, I., et al., Lancet (1972) 2:1175-1177; Dougherty, T,J,, et al., Cancer Research (1978) 38:2628-2635; Dougherty, T,J,,, et al,,, The Science of Photomedicinell (1982),, J,D, Regan and J.A. Parrish, eds.; Dougherty, T.J., et al., Cancer: Principles and Practices of Oncology (1982) B,T. DeVita Jr, et al., eds.) An improved photosensitizer which is prepared from HPD by adjustment of. . . recovery of the aggregate is disclosed in U.S. patent 4,649,151, incorporated herein by reference. The purified form of the mixture is called dihematoporphyrin ether (DHE) in the patent and is marketed under the trademark Photofrini., II.

This has been used, as described in U.S, patent 4,649,151 in a manner completely analogous to HPDe

Other porphyrin-type photosensitizers have also been reportedt including various chlorophyll derivatives derived from both bacteria and higher plants, A group of compounds of particular interest. . . assignee, and incorporated herein by reference. These compounds are so designated because they absorb light at longer wavelengths than that absorbed by hematoporphyrin derivative or its related compounds, and therefore these porphyrins appear green in white light. The green porphyrins are derived from protoporphyrin-IX by a reaction with a single acetylenic dienophile in a Viels-Alder reaction, and optional subsequent rearrangement and/

or reduction, A subset of green porphyrins, designated herein benzoporphyrin derivatives (BPD) are particularly useful among this group.

All of the porphyrin-type photosensitizing compounds described in the literature are generally useful in the same manner as hematoporphyrin derivative as set forth in the above-cited art. In addition, however, to in

vivo therapeutic and diagnostic protocols for tumors, as described above, these compounds can be used in other in vivo and in vitro applications, For example, these photosensitizers are useful in. . .

4,512,762 and 4,577,636. U.S. patent nos. 4,500,507 and 4,485,806 describe the use of radiolabeled porphyrin compounds, including HPD, for tumor imaging, U,S. patent no, 4,753,958 describes the use of topical applications of porphyrin sensitizers for diagnosis and treatment of skin diseases, U.S, patent no, 4,748,120 describes the use of photosensitizers in the treatment of whole. . . treatment of blood and components
is also described in U,S. patent no. 4,727,027 where the photosensitizer is furocoumarin and its derivatives, rather than porphyrin-type materials, In addition, viruses are inactivated in therapeutic protein compositions in vitro as disclosed in U.S. patent no. 4,268,947.

For the administration of the porphyrin related photosensitizers in in vivo applications, various pharmaceutical compositions have been suggested. In one approach, the photosensitizing drug was coupled to antibodies which putatively enhance the ability of the drug to localize in the desired target cell. For instance, HPD was coupled to antibodies directed to the murine myosarcoma cell line Ml as described by Mew, D., et al., J Immunol (1983) 130:1473 HPD was also conjugated to CAMAL-1 antibodies which are directed to a human leukemia
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antigen (Mew, D,, et al,, Cancer Research (1985)]45:4380-4386). The conjugation of chlorin e6 to anti T-cell monoclonal antibody was described by Oseroff, A,R., et al,, Proc Natl Acad Sci USA (1986) 83:8744
The use of liposomes or lipoproteins as pharmaceutical. . .

Dis]closure of the Invention
The invention provides pharmaceutical compositions which are useful in solubilizing porphyrin-type photosensitizers and in providing a means for effective administration of these drugs, as well as facilitating the linkage of these photosensitizers into a complex with a targeting agent, The photosensitizing porphyrin-type compounds are conjugated to a hydrophilic polymer in a suitable ratio of photosensitizer to polymer to permit the solubilization of the sensitizer and effective administration thereof; it addition the polymer can further be coupled to a targeting moiety to result in a conjugate wherein both targeting agent and photosensitizer retain maximal activity.

. . .
this invention
provides pharmaceutical compositions useful for
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facilitating the targeted delivery of pharmaceutical agents generally. These compositions include an active pharmaceutical agent conjugated to a hydrophilic polymer together with a targeting moiety.

. . .
aspect, the invention is
directed to pharmaceutical compositions useful in photodynamic therapy or related methodologies, which

compositions contain as an active ingredient a conjugate of a porphyrin-type photosensitizer with a water soluble, multifunctional hydrophilic polymer. The ratio of photosensitizer to polymer will be variable depending on the particular circumstances, and. . .

. . .

the invention is directed to pharmaceutical compositions which contain complexes wherein the water soluble, multifunctional, hydrophilic polymers such as those described above are conjugated both to a photosensitizing drug derived from porphyrin and a targeting agent which effects homing of the complex to the desired cell or tissue, Such targeting agents include antibodies or fragments thereof, receptor ligands, and generally any ligand which specifically binds to a surface characteristic of the target cells.

Additional aspects of the invention are directed to the conjugates per se and to methods to conduct photodynamic therapy and related methodologies using the compositions and conjugates of the invention. These methodologies include both in vivo administration of the compositions and conjugates and the extracorporeai treatment of biological fluids, including blood and blood products for use in clinical applications, or in extracorporeal treatment for. . .

. . .

the invention is directed to pharmaceutical compositions which contain complexes wherein a water soluble, multifunctional, hydrophilic polymer such as those described above is conjugated both to an active drug and a targeting agent which effects homing of the complex to a desired cell or tissue where the drugfs action is desired. Such targeting agents include antibodies or fragments thereof, receptor ligandSr and generally any ligand which specifically binds to A surface characteristic of the target cells. Additional aspects of the invention are directed to these drug-polymer-targeting agent conjugates per se and to methods to conduct therapy using the compositions and conjugates of the invention. These methodologies include both in vivo administration of the compositions and conjugates and the extracorporeal treatment of biological fluids, including blood and blood products for use in clinical applications, or in extracorporeal treatment for readministration to. . .

Brief Description of the Drawings

Figure 1 shows the generic structures of green porphyrins, one group of photosensitizers useful in the conjugates of the invention.

Figure 2 is a flow diagram for the coupling of photosensitizer to PVA.

Figures 3A and 3B show comparative spectra of conjugated and unconjugated photosensitizers of the invention; Figure 3A relates to BPD-MA and its conjugate; Figure 3B relates to DHE and its conjugate.

Figures 4A, 4B and 4C show comparisons of the cytotoxicity of the conjugated and unconjugated photosensitizers of the invention using BPD-MA or DHE conjugates on A549 and A431 cells. Figure 4D shows a

comparison of the cytotoxicity of the conjugated and
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unconjugated photosensitizers of the invention using BPD-MA on P815 cells,
Figures 5A and 5B show a comparison of the biodistribution of the conjugated and unconjugated forms of the photosensitizing drugs after 3 hours and 24 hours, respectively,
Figure 6 outlines the conjugation of antibody to carrier,
Figure 7 shows an elution profile of a conjugate of the invention which includes BPD-XA and monoclonal antibody T48 both conjugated to carrier.

Figure 8 shows the retention of immunoreactive activity by T48 antibody in the conjugates of the inven-
tion.

Figure 9 shows the cytotoxicity of the BPD-MA conjugated to carrier.

Figures 10-14 show the retention of activity and specificity of action of a representative drug, BPD-MA, conjugated to a carrier together with 5E8 monoclonal antibody targeting agent.

Modes of Carrying Out the Invention
The invention employs conjugates of hydrophilic polymers with photosensitizing compounds which are porphyrins or porphyrin related. one major advantage of such conjugates, besides conferring solubility on the drug, is the facilitation of formation of complexes which contain both photosensitizing drug and targeting agent.
. . .
activity. A wide variety of each of these components is available for use in the compositions of the invention. In addition, the conjugates both of drug and carrier alone and those including homing moieties such as antibodies or receptor ligands can be further
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reacted with additional components such as labels or other cytotoxic elements, In other modes, the invention employs these aspects to conjugate and deliver other active agents beyond the photosensitizers.

The Photosensitizer
The photosensitizers of the invention are porphyrin-type photosensitizers as are generally known and employed in the art. A number of references describing some of these compounds are cited in the background section above. By far the largest body of experimental work has been conducted on the improved form of hematoporphyrin derivative (HPD) which is a composition whose preparation is described in the above cited Dougherty patent 4,649,151. This material is referred to herein for convenience in the same manner as described in that patent, as dihematoporphyrin ether (DHE) although it is understood that the mixture prepared as described contains numerous additional components many of which are active photosensitizers. Thus, as used herein,, DHE refers specifically to the described mixture rather than an individual compound or mixture of compounds limited to dihematoporphyrin ethers per se.

An additional group of compounds which has been found extremely useful in photodynamic therapy and related methodologies is the green porphyrin (Gp) group having the basic structure outlined in Figure 1. These compounds are prepared by a Diels-Alder reaction with the substrate related to protoporphyrin-IX, resulting in an adduct to the A or B ring as shown. As Figure 1 showSr the direct product of the addition,. . . the diene is unconjugated. Rearrangement of the compound of formulas 1 or 2 to the compounds of formulas 3 or 4 results in conjugation of the pi-bonds in the fused cyclohexadiene.

The compounds of general formulas 3 and 4 are referred to SUBSTITUTE 5HEET herein as benzoporphyrin derivatives or BPD. 9 These compounds are named specifically as the compounds of formulas 3 and 4 appear to be the most. . .

. . .

aryl--i.e., phenyl optionally substituted as above-defined,

As shown in Figure 1, the adduct formed by the 1 2 reaction of R C=C.R with the protoporphyrin-IX ring system (R3 is a protected form of 2-carboxyethyl such as 2-carbomethoxy ethyl or 2-carboethoxy ethyl; R 4 is CH=CH 2) are compounds. . . change the absorption spectrum of the resulting compound, The product of the Markovnikov addition of water provides a substituent structure analogous to the hematoporphyrin ring system at the relevant ring. Thus, SUBSTITUTE SHEET the compounds of the invention include various groups as R including substituents which provide additional porphyrin or porphyrin-related ring systems, as will be further described below.

R3 in protoporphyrin-IX is 2-carboxyethyl (-CH CH COOH), However, the nature of R 3 (unless it 2 contains a pi-bond conjugated to ring pi-bond), is ordinarily not relevant to the progress of the Diels-Alder reaction or to the effectiveness and absorption spectrum of the. . .

. . .

with the reaction, Thus, the Diels-Alder reactions described by Morgan et al. and by Pangka et al. utilized the dimethyl ester of protoporphyrin-IX as a substrate in order to prevent interference with the reaction by the free carboxyl group and to provide suitable solubility characteristics.

Porphyrin related compounds in general, and, in particular, these BPD embodiments which contain -COOH may be prepared as the free acid or in. . .

Four particularly preferred compounds useful in the conjugates herein are collectively designated benzoporphyrin derivative (BPD) as they are forms of Gp having the formula 3 or 4. In these compounds R 1 and R2 SUBSTITUTE. . .

In general, the porphyrin-type

photosensitizers useful in the conjugates of the invention contain a tetrapyrrole-type nucleus. This nucleus is a four-ring system of the skeleton.

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HN
which is highly conjugated. It includes the porphyrin system, which is, in effect, a completely conjugated system, the chlorin system, which is, in effect, a dihydro form of the porphyrin, and the reduced chlorin system,
which is a tetrahydro form of the completely conjugated system, When porphyrin is specified, the completely conjugated system is indicated; Gp is effectively a dihydro form of the porphyrin system.

Thus, the porphyrin-type photosensitizer is defined as any photosensitizing compound which contains sufficient conjugation in the tetrapyrrole ring system as described above to absorb an effective amount of light in the visible or near-ultraviolet region to. . .

The Hydrophilic Polymer Carrier
The hydrophilic polymer to which the photosensitizing porphyrin-type compound is conjugated is
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generally an addition or condensation polymer with multiple functionality to permit the conjugation described. The functional groups ordinarily found on the porphyrin.type photosensitizers are common oxygen or nitrogen containing substituents; targeting agents often also contain -SH groups. Accordingly the functionality of the carrier must be. . .

Second, the carrier is preferably capable of conjugation to a multiplicity of moieties, both photosensitizing moieties and targeting agents.
. . .
the composition
should have a multiplicity of functional groups which can be used per se, or which can be derivatized to other intermediate linkers to effect the covalent association of the photosensitizing drug and, if desired, the targeting agent. Suitable functional groups for such conjugation include hydroxyl groups, sulfhydryl groups, amino groups, carboxyl groups, aldehyde groups, and the like. Some of these are preferable to others because of. . .

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One class of polymers which is useful in the conjugates of the invention comprise the polysaccharide polymers. Low molecular weight polysaccharides such as dextran, sepharose, or polyribose, polyxyloser and the like make suitable. . .

The molecular weight of the polymer is arbitrary, but generally the polymers forming the conjugates of the invention must have sufficient monomeric units so that there hydrophilicity is not destroyed when certain of the functional groups are. . .
. . .
bound
to the carrier independent of each other and the activity

of the individual components is thereby preserved. In particular, the invention includes conjugates wherein, in addition to the photosensitizing drug, specific targeting agents are coupled. In utilizing this approach, the photosensitizing activity of the drug is retained and the targeting agent does not suffer significant loss of. . . . .
portion
thereof or a ligand specific for receptor can be used as a target specific component. The immunoglobulin can be polyclonal r monoclonal antibody and may comprise whole antibodies or'immunologically reactive fragments of these antibodies such as F(abl)2r Fabr or Fabf fragments. Use of such immunologically reactive fragments as substitutes for whole antibodies is well known in the art. See, for example, Spiegelberg,, H,L., in Immunoassays in the Clinical Laboratory (1978) 3:1
The ligand specific. . .

Preparation of the Conjugates
The conjugates of the invention comprise the above-described hydrophilic polymer coupled with a porphyrin-type sensitizing drug. They may further contain a targeting agent as described in the previous section.

Methods for forming these conjugates are commonly practiced and a variety of approaches may be used depending on the nature of the polymer chosen, the nature of the functional groups available in the photosensitizer, and the approach chosen for conjugation of the targeting agent. In some instances, it may be useful to provide spacing between the immediate polymer backbone and the functional group to be covalently linked to photosensitizer or targeting agent. For example, 1,6-diaminohexane can be used as a spacer, as illustrated below. Generally, however, the spacer contains. . . of
binding the functionality on the hydrophilic polymer and a functionality capable of binding to the photosensitizer or targeting agents,
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In providing the conjugates of the invention, a multiplicity of photosensitizing moieties is conjugated to the polymer; typically the range is 500:1 to 1:1 of phosensitizer:carrier. Preferred are ratios of 75:1-10:1, 10:1 is especially preferred. Preferred ratios. . .

Thus, depending on the nature of the functional groups used to conjugate the photosensitizer and optionally the targeting agent, a variety of conjugation techniques can be used. General means to conjugate the functionalities of the attached moieties and the hydrophilic polymer carrier will be known to those of ordinary skill in the art, In addition to direct conjugation, bifunctional linkers can be used, such as the
diamine illustrated below, aldehydes such as glutaraldehyde, or other homobifunctional linkers, as well as commercially available more complex homo- and heterobifunctional linkers such as those manufactured by Pierce Chemical Company, Rockford, IL. The types of conjugation linkages used can include formation of disulfides, addition of sulfhydryls to pi-bonds, formation of amides, esters, hydrazones, and the like.

Taken generally, this invention provides a pharmaceutical composition comprising as an active ingredient a hydrophilic, water-soluble, multifunctional carrier with which is conjugated an active agent, In some preferred embodiments this active agent is a photosensitizer. In other preferred embodiments, this carrier is additionally conjugated with one or more target specific components. In this descrption, wherein the polymer, target compositions, various linking groups, spacers, and methodologies of preparation and use are set forth with specific reference to photosensitizers, these teachings can be adapted and applied. . .

These materials can be formed by the general process of
. conjugating an active agent or active agent precursor to a first portion, which is some but not all, of the present or potential reactive sites on a hydrophilic water-soluble polymer, and
- conjugating a target-directing group or component to a second portion of the reactive sites present in the polymer.

As has been set forth, this proportional conjugating can be carried out by controlling the conditions of the first conjugating to not involve all the sites on the polymer; or it can be carried out by temporarily blocking, and thus temporarily reserving a portion of the sites prior to and through the first conjugating, or it can be carried out by providing a plurality of types of reactive sites on the polymer and using one type of site for conjugating to the active agent and another for conjugating to the target-directing group,
Additional Components
In addition to the required photosensitizer and hydrophilic backbone, certain additional components may be coupled to the conjugate. These include label, additional
cytotoxins and other functionalities which may be useful in the applications herein.

The conjugates of the invention may be further derivatized to a compound or ion which is a label. A wide variety of labeling moieties. . . used, including radio-
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isOtOPesr chromophores, and fluorescent labels. Radio-isotope labeling in particular can be readily detected in vivo. Radioisotopes may be coupled by coordination as cations in the porphyrin system. Useful cations include technetium, gallium, and indium. In the conjugates, either the porphyrin or the polymer can be linked to or
associated with label,
In general, the conjugates can also be administered or used in in vitro methods when complexed to appropriate metal ions. As is generally understood in the art,. . . nature
and desirability of the inclusion of a metal ion in the tetrapyrrole-type nucleus depends on the specific application for which the conjugate is intended. When the inclusion of a metal ion is desired, the desired meta ion can be inserted using the appropriate. . . under known conditions. For example, zinc ion can be introduced by treating the compound with zinc acetate in 1:1 methylene

chloridetmethanol,
Administration and Use
The conjugates of the invention are thus useful in general, in the manner known in the art for hematoporphyrin derivative and for DHE. These materials are useful in sensitizing neoplastic cells or other abnormal tissue to destruction by irradiation either 'in vivo or ex vivo using visible light--upon photoactivation, the photosensitizer has. . . it to singlet oxygen. This singlet oxygen is thought to be responsible for the cytotoxic effe-ct. In addition, the photoactivated forms
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of porphyrin fluoresce, which fluorescence can aid in localizing tumors or other sites to which the conjugates
home.

Typical indications, known in the art, include destruction of tumor tissue in solid tumorst dissolution
of plaques in blood vessels (see, e.g., U,S. Patent 4,512,762); treatment of topical conditions such as acne, athletefs foot, warts, papilloma, and. . .

The conjugates of the inventions are formulated into final pharmaceutical compositions for administration to the subject or applied to an in vitro target using techniques. . .

The conjugates can be used in the systemic treatment of tumors and neoplastics made as bronchial,
cervical, esophageal or colon cancer and for the diagnosis of same. They can be administered systemically, in particular by injection, or can be used topically. They can be. . .

For diagnosis, the conjugates may be used alone or may be labeled with a radioisotope or other detecting means.

If treatment is to be localized, such as for the treatment of superficial tumors or skin disorders, the active conjugates may be topically administered using standard topical compositions involving lotions, suspension, or pastes.

The quantity of conjugate to be administered depends on the choice of active ingredient, the condition to be treated, the mode of administration, the individual subject, and. . .

The wavelength of irradiating light is preferably chosen to match the maximum absorbance of the porphyrin-type photosensitizer. For BPD-MA and BPD-DA, the preferable wavelength is between about 680 and 700 nm.
. . .
, and preferred irradiation dosage rates are in the range of 100-300 mW cm -21
In addition to in vivo use, the conjugates of the invention can be used in the treatment of materials in vitro to destroy harmful viruses or infectious agents.
. . .
In addition, biological products

such as Factor VIII which are prepared from biological fluids can be irradiated in the presence of the conjugates to destroy contaminants.

Example 1
Preparation of PVA/Photosensitizer Conjugates
Two photosensitizers were used for conjugation to polyvinyl alcohol (PVA), A DHE mixture was obtained as the commercially available Photofrinv II from Quadralogic Technologies Inc., Vancouver, B.C. As described above, this is the mixture obtained when hematoporphyrin derivative is treated as described in U.S. Patent 4r649,151, The other is designated BPD-MA which is the 1 2
compound of formula 3 wherein. . . is 2-carboxy ethyl. The compound is supplied as
a3mixture of the two isomers having a single hydrolyzed R . The procedure for conjugation is outlined in Figure 2.

To conjugate the photosensitizers with PVA, the alcohol groups were modified to provide amino reactive groups as follows: a complex was formed between pyridine and. . .

The crude product was dialyzed (MW cutoff 12 kd-14 kd) in 4 liters of distilled water (four changes). The modified PVA conjugate (M-PVA) was lyophilized and 700 mg of solid brown powder was obtained. The M-PVA prepared according to this protocol contained about 60%. . .
. . .
with
2 ml distilled water. The preparations were then dialyzed against distilled water at 4 0C, and the concentration of photosensitizer in the conjugates was analyzed spectrophotometrically. The ratios were estimated at 100:1, 75:1, 50:1, 25:1, and 12:1, respectively, BPD-MA to M-PVA. By suitable adjustment of proportions, varying
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amounts of BPD-MA can be coupled to the polymer. All reactions and handling were in the dark, and the final solutions were lyophilized. Conjugates can readily be separated from unreacted BPD-MA chromatographically.
. . .
more than 95%. The final products were kept in Drierite at 40C in the dark,
Similarly, DHE was treated with M-PVA to produce conjugates with ratios of 50:1, 25:1r 12:1 of DHE to M-PVA,
To test stability, the conjugates were dissolved in pH 4o2lf 7.26 and 8.42 buffers at 0.064 mM and stored at various temperatures: -200C,, 40Cr 200C and 370C. TLC analysis was used to monitor any dissociation; only the conjugate maintained at pH 8.42 at 370C showed dissociation at 4 weeks. After this period, slight dissociation was observed in all preparations,
Figures 3A and 3B show comparative spectra of conjugated and unconjugated BPD-MA and DHE, respectively.

Example 2
Cytotoxicity of the Conjugates
Adherent human lung cancer cell lines A549 and A431 were grown to log phase and cells were harvested with 10% trypsin and vigorous agitation. A final. . . plated (100 ul) into

96 well
Immulon II plates and incubated overnight, On each plate, standard concentrations of DHEI BPD-MA, or the respective conjugates dissolved in MEM plus 5% FCS were tested in triplicate. Controls of cells not exposed to porphyrin were run on each plate.

. . .

hour, Cell viability was determined using an MTT assay (Mosmannr Tor J Immunol Methods (1983) 65:55-63). The percentage killed was calculated for each porphyrin Concentration, and the LD 50 of the cell line determined. The results of this assay are shown in Figures 4A-4C.

Figure 4A shows these results for BPD-MA both alone and in conjugates of various ratios using A549 cells in the test. Figure 4B shows an analogous determination on A549 cells using DHE both in unconjugated form and conjugated to the modified PVA at various levels. Figure 4C shows analogous results for the DHE and its conjugates using A431 cells in the assay. As shown, there are no significant differences in the phototoxicity of the porphyrins alone compared to the conjugated materials. No significant differences between various ratios between 12:1 and 50:1 were found.

similarly, a nonadherent murine mastocytoma cell line, P815, described by Richter, A,M,, et al., J Nat'l Cancer Inst (1987) 79:1327-13311 was used as a cytotoxicity test subject. Cells in log phase were incubated for one hour at 370C with a range of either BPD-MA alone or BPD-MA conjugate in the absence of serum.

. . .

MTT assay 18 hours after light irradiation. The results are shown in Figure 4D. There were no significant differences between the porphyrin and the conjugate in phototoxicity, although it appears that the conjugate is slightly more effective.

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Example 3

Biodistribution of the Conjugates

A preparation of BPD-MA/M-PVA at a25:1 ratio was prepared as described in Example 1 using tritiated BPD-MA and used to follow biodistribution of this conjugate in DBA/2 mice bearing subcutaneous P815 tumors,

The procedure is described in Richter, A,M,, et al,r 5 J Photochem Photobiol (1989), Briefly, lxlO P815 cells were injected subcutaneously in the right flank. Fifteen days later, when the tumors were 8-12 mm in diameter, the mice were injected intravenously with a 0.2 ml containing 12A ug of BPD-MA or the PVA conjugate containing an equivalent amount of BPD, a specific activity of 5.56 uCi/mg. The animals were sacrificed at 3r 24 and 48 hours post-injection. . .

Both the conjugate and the BPD-MA alone show high tumor/tissue ratios in various organs, especially in muscle and brain. The conjugate is fairly consistently superior to the unconjugated BPD-MA in tumor specificity.

Example 4

Preparation of Target-Specific Conjugates
A conjugate of BPD-MA with PVA having a ratio of BPD:PVA of 25:1 was prepared using the PVA described in Example 1 and the methodology set forth therein. The conjugate was then reacted with 3-mercaptopropionic acid in the presence of ECDI in DMSO to obtain a product having the mercapto-containing acid moiety contained at 2-3 reactive sulfhydryls per carrier molecule. The sulfhydryl-derivatized conjugate was then treated with the monoclonal antibody T48, specific for human chorionic gonadotropin which had been conjugated to the commercially available heterobifunctional linker, sulfo-M-maleimidobenzoyl-N-hydroxysulfosuccinimide ester (SMBS, Pierce Chemical
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Company, Rockford, IL). The maleimide moiety reacts directly with the sulfhydryl group to obtain a linked conjugate through a thioether bond to the linker. The
steps in this procedure are outlined in Figure 6.

In more detailr preliminary experiments established that molar ratios of 10:1 for the 3-mercapto-propionic acid (MPA):M-PVA-BPD-NA in the reaction mixture resulted in. . . reaction was stirred for 4 hours at room temperature under argon, and then dialyzed against 0.01M acetate buffer, pH 5
The monoclonal antibody T48 at 9,615 mg/ml was dialyzed against 0.01M carbonate buffer, pH 8.5; SMBS was added to this buffer in a 30-fold molar. . . stirred for two hours after which it was
washed through centricon-30 and the buffer was changed to 0,61M acetate, pH 5,5*
The T48-SMBS conjugate and the M-PVA-BPD-MA were mixed in equimolar concentrations in 0.01M acetate buffer, pH 5.5, stirring gently for 18 hours at 4 0C. The resulting conjugate was concentrated by dialysis against polyethylene glycol.

The resulting conjugates containing both the T48 antibody and the BPD-MA photosensitizer were recovered from the reaction mixture and chromatographed on Sepharose CL-4B. The concentrated samples were made up to 0.5% w/v 2,000 MK PVA for application to the column to prevent unwanted adsorption of the conjugate, and then applied in 1 ml portions to a column of bed volume 68.4 ml, equilibrated with 01M acetate buffer, pH 5. . . and 688 nm using an LKB Ultra-
spectrophotometer 4050. The elution pattern is shown in Figure 7, As the pattern shows, the conjugated material elutes as a defined peak at an elution volume of approximately 50 ml. Covalent binding of the T48 to the carrier system. . .

Example 5
Activity of Target-Specific Conjugates
The eluted, purified conjugates were then assayed for ability of the antibody to bind antigen and for the cytotoxicity with respect to Ml cells as compared to the free antibody or photosensitizer.

To determine the specific activity of the T48 antibody, Immulon II ELISA plates were coated with human chorionic gonadotropin (HCG) antigen at 5 ug/ml in a volume of 100 ul per well in 0.1M bicarbonate buffer,

pH 9 Test samples containing T48 in conjugated and unconjugated form were added in serial dilutions to the wells, and plates were developed with alkaline phosphatase labeled rabbit-antimouse Ig obtained from. . .

The results of an ELISA assay showing the binding of conjugate to antigen in comparison to unconjugated antibody are shown in Figure 8. As shown in Figure 8, the concentration curve for the conjugated antibody tracked that of the antibody in unconjugated form. In these curves, the starting concentration was 1 ug/ml and a two-fold dilution series was used.

The cytotoxicity assays were conducted as described by Richter, A.M., et al. (1979) J. Nat'l Cancer Inst. 79:1327 Briefly, M-1 tumor cells, in single cell suspension, obtained from a freshly prepared excised subcutaneously grown tumor were plated in 96 well Falcon

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plate in 200 ug DME (Gibco) containing 10% FCS at a concentration of 10 5. . . changed, and at 48 hours, the cells were washed and then incubated with various concentrations of BPD-MA, with M-PVA-BPD-MA and with the antibody-M-PVA-BPD-MVA conjugate for 1 hour at 370 C, in the dark, in the absence of serum. Following the incubation, cells were exposed to light. . . results are shown in Figure 9, Again, the ability of the photosensitizing drug to effect cell killing was substantially unaffected by its conjugation to either modified PVA per se or the conjugate containing target-specific agent.

Example 6
Preparation and Testing of
Additional Target-Specific Conjugate

A conjugate of BPD-MA was formed with PVA and this conjugate subsequently conjugated to 5E8 monoclonal antibody,.to yield a target-specific conjugate.

Monoclonal Antibodies. The 5EB monoclonal antibody reacts with a cell surface glycoprotein associated with human squamous cell carcinomas of the lung but not with normal lung tissue. The monoclonal antibody was purified from ascites fluid. The control, T48 (Quadra Logic TechnologieSr Vancouverr Canada), has specificity for another antigen, human chorionicgonadotropic hormone (hcg, Sigma, St.. . .

Conjugation Procedures. The procedures used for producing immunoconjugates involved the formation intially of conjugating BPD to a hydrophilic carrier, modified polyvinyl alcohol (PVA, Aldrich Chemical Co., Milwaukee, WI) substantially as shown in Example 1 and Figure. . . . . PVA is readily amenable to reaction with the free carboxyl group of BPD, in the presence of carbodiimide. We have found that PVA-BPD conjugates with varying PVA:BPD ratios could easily be produced by altering molar ratios. In the present example molar ratios of PVA:BPD were 1:25. . . to carry out this step. This carrier system (PVA-BPD-SH) can be prepared and characterized in bulk and then

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used for conjugation with a variety of monoclonal antibodies using the heterobifunctional linker sulfo-M-
maleimidobenzoyl-N-hydroxysulfosuccinimide ester (SMBS, Pierce, Rockford, IL), SMBS was reacted with the antibody in question by mixing at a molar ratio of 30:1 (SMBS:MoAb) in carbonate buffer, pH 8,5, This resulted in the presence of 2-3 SMBS groups being bound per molecule of antibody. Final conjugation between the PVA-BPD-SH carrier system and the MoAb was effected by mixing the two reactants at a 1:1 molar ratio in acetate buffer, pH 5
Separation of Conjugates by Gel Filtration. The conjugated product was separated from unconjugated reactants by passage of the material over a Sepharose CL-4B (Pharmacia LKB, Uppsala, Sweden) column. Eluted material. . . strongly only at 280 nm and eluted at 28-35 ml. This latter was shown to elute in the same position as free antibody. The material eluting at 15-27 ml was assumed to be conjugated and was collected and used for further testing.

SDS-PAGE Analysis of Unlabeled and Tritiated Conjugates, Material assumed to be conjugated and collected from Sepharose CL-4B columns was subjected to analysis by reducing SDS-PAGE to determine whether material containing protein and BPD were really covalently linked. Conditions for gel analyses were as follows.

Sepharose CL-4B column-purified conjugated materials were subjected to SDS-PAGE Analysis to determine whether material containing protein and BPD were really covalently linked, Samples containig either 3H-BPD-PVA-5EB or unlabeled BPD-PVA-5E8 were run in parallel on a 7.5% polyacrylamide reducing gel. The gel was run 30. . . Radioactivity was measured using a Beckman
liquid scintillation counter (Beckman Instruments, Fullerton, CA),
Cytotoxicity Assays. Standard assays, described by Richter et al. J Natl Cancer Inst (1979) 79:1327-13321 were used to determine the phototoxicity of BPD throughout the conjugation procedures. Briefly, A549 and M-1 cells were grown to log phase and cells were harvested with 10% trypsin and vigorous agitation. Cells. . . light density was 6 mW/cm as measured by YSI Kettering Model 265 radiometer, and the dose delivered was 21.6i/cm
ELISA Assays, The 5E8 antibody reacts in a standard cellular ELISA with A549 cells. Briefly, A549 cells were grown to confluence in 96-well Falcon plates.

Specific activity of 5E8 conjugate was tested through a cellular ELISA and the results showed that 80% of activity was retained, The activity of the BPD associated with.the 5E8 MoAb conjugate was determined using a standard cytotoxicity assay. The results (Figure 10) showed that the 5E8-PVA-BPD conjugate was equally as effective in killing cells as was either free BPD or the PVA-BPD carrier,
Further experiments were performed to determine whether 5E8-PVA-BPD conjugates would bestow enhanced delivery and photoxicity to targeted cell lines.

. . .
for 2 hr in the dark prior to exposure to light. The results (Figure 11) showed that under these condUtons, the MoAb conjugate was taken up less well by

the cells than either BPD on its own or PVA-BPD. This experiment was repeated, except that. . . was continued for 24 hr. This prolonged incubation enhanced
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photoxic killing in all preparations but did not improve selectivity with the MoAb conjugate in comparison to other BPD preparations (Figure 12). Similar experiments were carried out in the presence of 10% FCS- In one series (Figure 13) A549 cells in 10% FCS were incubated in the dark for 2 hr with BPD, the 5E8 MoAb conjugate or the control T48 MoAb conjugate. Under these conditions it appeared that good selectivity was shown by the 5E8 conjugate in comparison to control materials. In order to establish specificity, a further experiment was carried out using M-1 cells in 10% FCS. . . MoAb does not react with this murine cell line). The results- (Figure 14) show that there is no difference in phototoxicity between the conjugates (5E8 and the T48 control) indicating that the results of Figure 14 do establish the specificity of the 5E8 conjugate. These data provide evidence that the 5E8 conjugate can, under the parameters described here, deliver photosensitizer in both a selective and specific manner, to the designated target cell and-that the presence. . .

CLMEN le A pharmaceutical composition useful for photodynamic therapy which composition contains, as active ingredient, a conjugate of a porphyrin-type photosensitizer with a hydrophilic, water soluble, multifunctional polymeric carrier, wherein the ratio of photosensitizer to carrier is 1:1 to 500:1.

5 The composition of claim 1 wherein the porphyrin-type photosensitizer comprises a green porphyrin of formulas 1-6 of Figure 1 wherein each R 1 and R2 is independently selected from the group consisting of carbalkoxy (2-6C), alkyl. . .

6 The composition of claim 5 wherein the green porphyrin is of formula 3 or 4 in Figure 1 and wherein each R 1 and R2 is independently carbalkoxy (2-6C) and. . .

7 The composition of claim 1 wherein the porphyrin-type photosensitizer is DHE or active component thereof.

10 A pharmaceutical composition useful for photodynamic therapy which composition contains, as active ingredient, a conjugate of a porphyrin-type photosensitizer with a hydrophilic, water soluble, multifunctional polymeric carrier, wherein the ratio of photosensitizer to carrier is 1:1 to 500:1, which conjugate further contains a target specific component also conjugated with the carrier,

13 The composition of claim 12 wherein said target specific component is a monoclonal antibody.

14 The composition of claim 1 further characterized by its activity of imparing the function of target cells or viruses when said. . . viruses are contacted with an effective amount of the composition of claim 1 in a manner which permits the accumulation of the

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conjugate in said cells or viruses, followed by irradiating said cells or viruses with an effective amount of radiation at a wavelength absorbed by the photosensitizer contained in the conjugate for a time and intensity sufficient to impair said cells or viruses.

15 The composition of claim 14 wherein said cells are cancer cells.

. . .

or viruses are contacted with an effective amount of the composition of claim 1 in a manner which permits the accumulation of the conjugate in said cells or viruses, followed by irradiating said cells or viruses with an effective amount of radiation at a wavelength absorbed by the photosensitizer contained in the conjugate for a time and intensity sufficient to impair said cells or viruses.

19 The composition of claim 18 wherein said cells are cancer cells.

22 A pharmaceutical composition useful for therapy which composition contains, as active ingredient, a conjugate of an active agent with a hydrophilic, water soluble, multifunctional polymeric carrier, wherein the ratio of active agent to carrier is 1:1 to 500:1, which conjugate further contains a target specific component also conjugated with the carrier.

25 The composition of claim 23 wherein said target specific component is a monoclonal antibody.

29 A method for preparing a target specific pharmaceutically active conjugate comprising conjugating a pharmaceutically active agent to a hydrophilic, water soluble, multifunctional polymer
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carrier at a ratio of agent to carrier of 1:1 to 500:1 thereby yielding an intermediate product and conjugating a target specific component to said carrier in said intermediate product.
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=> d his

(FILE 'HOME' ENTERED AT 09:21:36 ON 15 AUG 2006)

FILE 'REGISTRY' ENTERED AT 09:21:49 ON 15 AUG 2006
E "M-THPC"/CN 25
E "THPC"/CN 25
E "MTHPC"/CN 25
L1 1 S E3

FILE 'CAPLUS' ENTERED AT 09:22:56 ON 15 AUG 2006
L2 296 S L1
L3 468489 S ANTIBOD? OR IMMUNOCONJUGAT?
L4 13 S L3 AND L2
L5 3 S L2 (L) L3
L6 2 S L4 NOT PY>1999

FILE 'PCTFULL' ENTERED AT 09:24:55 ON 15 AUG 2006
L7 396 S MTHPC OR (M () THPC) OR EF 9 OR FOSCAN OR TEMOPORFIN

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L8         90279 S ANTIBOD?
L9           304 S L8 AND L7
L10           16 S L9 NOT PY>1999
L11       520275 S CONJUGAT? OR IMMUNOCONJUGAT? OR COUPL? OR LINK?
L12           16 S L11 AND L10
L13         2910 S PHOTODYNAMIC OR PDT
L14            8 S L13 AND L12
L15         4618 S ?CHLORIN OR ?PORPHYRIN
L16            0 S L5 AND L13
L17          922 S L15 AND L13
L18          353 S L13/AB
L19          251 S L18 AND L15
L20          124 S L19 AND L8
L21          119 S L20 AND L11
L22           33 S L21 NOT PY>1998
L23       100308 S CANCER? OR TUMOR? OR NEOPLAS?
L24           33 S L23 AND L22
L25          734 S L15/CLM
L26           11 S L24 AND L25
L27        34879 S L8/CLM
L28           10 S L24 AND L27
L29            2 S L28 AND L26

=> s phenyl
          90826 PHENYL
            702 PHENYLS
L30       90908 PHENYL
                (PHENYL OR PHENYLS)

=> s l28 and l30
L31            4 L28 AND L30

=> d kwic phenyl 1-4
'PHENYL' IS NOT A VALID FORMAT FOR FILE 'PCTFULL'

The following are valid formats:

ALL, MAX--------BIB plus IND plus ABS plus TX
ALLG------------ALL, MAX plus GI
BIB-------------AN, ED, UP, EW, UW, TIEN, TIFR, TIDE, TIES, IN, PA, LA, LAF
                DT, PI, DS, AI, PRAI
BIBG------------BIB plus GI
IND, IPC--------ICM, ICS
ABS-------------ABEN, ABF, ABFR, ABDE, ABES
TX--------------DETD, CLM
IALL,IMAX-------ALL indented with text labels
IALLG,IMAXG-----IALL, IMAX plus GI
DALL------------Delimited ALL format
STD-------------BIB plus IND
STDG------------STD plus GI
ISTD------------STD indented with text labels
ISTDG-----------ISTD plus GI
BRIEF-----------BIB plus ABS
BRIEFG----------BIB plus ABS plus GI
IBRIEF----------BRIEF indented with text labels
IBRIEFG---------IBRIEF plus GI
SCAN------------TI (random display without AN)
TRIAL (TRI)-----FA, TI, CLMN, DETN
SAMPLE (SAM)----FA, TI, CLMN, DETN
FREE------------FA, TI, CLMN, DETN
ENTER DISPLAY FORMAT (STD):end

=> d ibib 1-4
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L31 ANSWER 1 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997046262 PCTFULL ED 20020514
TITLE (ENGLISH): MEMBRANE INCORPORATION OF TEXAPHYRINS
TITLE (FRENCH): INCORPORATION DE TEXAPHYRINES DANS UNE MEMBRANE
INVENTOR(S): YOUNG, Stuart, W.;
WRIGHT, Meredith;
SESSLER, Jonathan, L.;
MODY, Tarak, D.;
MAGDA, Darren
PATENT ASSIGNEE(S): PHARMACYCLICS, INC.;
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM;
YOUNG, Stuart, W.;
WRIGHT, Meredith;
SESSLER, Jonathan, L.;
MODY, Tarak, D.;
MAGDA, Darren
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9746262	A2	19971211

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1997-US9501 A 19970604
PRIORITY INFO.: US 1996-8/657,947 19960604

L31 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997035617 PCTFULL ED 20020514
TITLE (ENGLISH): USE OF A TEXAPHYRIN IN PHOTODYNAMIC THERAPY OF PIGMENT-RELATED LESIONS
TITLE (FRENCH): UTILISATION D'UNE TEXAPHYRINE POUR LE TRAITEMENT PHOTODYNAMIQUE DES LESIONS PIGMENTAIRES
INVENTOR(S): WOODBURN, Kathryn, W.;
QUING, Fan;
YOUNG, Stuart, W.
PATENT ASSIGNEE(S): PHARMACYCLICS, INC.;
WOODBURN, Kathryn, W.;
QUING, Fan;
YOUNG, Stuart, W.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9735617	A1	19971002

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1997-US5332 A 19970326
PRIORITY INFO.: US 1996-8/624,311 19960326

L31 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1995021845 PCTFULL ED 20020514
TITLE (ENGLISH): TEXAPHYRIN METAL COMPLEXES HAVING IMPROVED FUNCTIONALIZATION
TITLE (FRENCH): COMPLEXES METALLIQUES DE TEXAPHYRINE A FONCTIONNALISATION AMELIOREE
INVENTOR(S): SESSLER, Jonathan, L.;
MODY, Tarak, D.;
HEMMI, Gregory, W.
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM;
PHARMACYCLICS, INC.;
SESSLER, Jonathan, L.;
MODY, Tarak, D.;
HEMMI, Gregory, W.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9521845	A1	19950817

DESIGNATED STATES
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UG US UZ VN KE MW SD SZ UG AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1995-US1996 A 19950215
PRIORITY INFO.: US 1994-8/196,964 19940215

L31 ANSWER 4 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1991014456 PCTFULL ED 20020513
TITLE (ENGLISH): IMPROVED COMPOSITIONS FOR PHOTODYNAMIC THERAPY
TITLE (FRENCH): COMPOSITIONS DE THERAPIE PHOTODYNAMIQUE AMELIOREES
INVENTOR(S): LIU, Daniel
PATENT ASSIGNEE(S): QUADRA LOGIC TECHNOLOGIES INC.;
LIU, Daniel
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9114456	A2	19911003

DESIGNATED STATES
W: AT AU BB BE BF BG BJ BR CA CF CG CH CM DE DK ES FI FR GA GB GR HU IT JP KP KR LK LU MC MG ML MR MW NL NO PL RO SD SE SN SU TD TG US
APPLICATION INFO.: WO 1991-CA93 A 19910322
PRIORITY INFO.: US 1990-498,042 19900322

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L31 ANSWER 2 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ABEN The present invention involves the use of a photosensitive texaphyrin for the photodynamic
treatment of a pigmented lesion, such as a melanodermic lesion, or of a lesion obscured by pigmented
tissue, such as. . . metallated with a
diamagnetic metal. Preferably, the texaphyrin is metallated with lutetium. Heretofore, melanoma has
been refractory to treatment with photodynamic therapy.

DETD . . . of the brain. Melanins
are also found in fungi, bacteria, and pathological human urine where they can be an

indication of melanotic tumors. These pigments are synthesized into the skin by
melanocytes; they have a broad absorption spectrum from 250 run - 1,200 nrn. . .

Of the skin cancers, melanoma causes the largest number of deaths. Because it
may act as a cocarcinogen or promoter, solar radiation may be related. . .

PDT has been successfully used for the treatment of cutaneous and
3 0 subcutaneous tumors (Dougherty, 198 1). However, pigmented melanomas have been
unresponsive, possibly due to poor light penetration into melanin-rich tissues (Pass,
1993), or due. . . scavenge free radical species; the latter ability also
limits the efficacy of ionizing radiation (Haylett el al., 1995). PDT using
3 5 hematoporphyrin derivative (HpD) has been successfully used in the treatment or
retardation of lightly pigmented and amelanotic melanomas (Dougherty, 198 1).

. . .
(Biolo et al., 1994). This naphthalocyanine is highly hydrophobic and requires the use of liposornes for solubilization. However,
0 silicon(IV)-naphthalocyanine displayed no tumor selectivity in a B16 murine melanoma
model, and tumor retardation that was not associated with thermal effects was
considered modest (Biolo et al., 1994). In studies performed with melanoma models,
human xenograft melanotic tumors were not responsive to PDT with PHOTOFRrNO II
(Nelson el al., 1988), despite containing more sensitizer than amelanotic melanoma. The
5 lack. . .

. . .
quantum
yield, and, since they are completely synthetic, can be modified so as to incorporate
5 desired properties. Texaphyrins have exhibited significant tumor selectivity as detected
by magnetic resonance imaging and fluorescence detection (Sessler el al., 1994; Young
et al., 1994). Texaphyrin compounds, methods for. . .

. . .
melanotic melanoma has not been very successful; pigmented melanoma appears resistant to ionizing radiation, and disseminated melanoma
5 is a very difficult tumor to treat, surgery being effective only when the tumor is localized.

. . .
to
the subject and photoirradiating the lesion. In an aspect of the invention, the pigmented
lesion may be a malignant lesion, a neoplasm, or other undesired pigmented cells and
other tissues, such as hair-containing lesions, or hair. In a preferred embodiment, the
malignant lesion is melanoma or other pigmented neoplasm.

ABBREVIATIONS

FCS fetal calf serum
HpD hematoporphyrin derivative
MST median survival time
PBS phosphate buffered saline
PDT photodynamic therapy
DETAILED DESCRIMON OF THE PREFERRED EMMODEMIENTS
The present invention provides for the use. . .

By melaniferous is meant containing melanin or other dark pigment. By melanoma is
2 0 meant a malignant neoplasm derived from cells that are capable of forming melanin. By
It melanin is meant a dark brown to black polymer of. . .
. . .
such as melaniferous tissue is meant
2 5 any lesion that may be a candidate for PDT including benign or malignant tumors,
melanotic or amelanotic, where tissue containing melanin or other pigment is physically
located in between a PDT light source and the lesion. . .

Cancer occurs more often in the skin than at any other site. Primary malignant
cutaneous tumors treatable by the present methods may arise from the epidermis, dermis,
or subcutaneous tissue or from any of the specialized cell types in the skin or its
1 5 appendages; malignant tumors that originate internally may eventually metastasize to the
skin. Certain premalignant dermatoses that are described as cytologically malignant, yet
biologically benign, may. . .

Malformations and tumors involving pigment-forming cells and treatable by the
present invention include ephelis (freckle), hair, Becker's nevus, and lentigo from
epidermal melanocytes; mongolian spot,. . .
. . .
derrr-]is, usually in
melanophages; the red color reflects inflammation associated with dilated dermal blood
vessels; and the white color is indicative of tumor regression with fibrosis. Melanomas
usually metastasize first via the lymphatic system, with involvement of regional nodes,
and then via blood vessels, with. . .
. . .
are
detectable by conventional methods, 70-85% of patients have distant metastases. The
sentinel node is the first node into which the primary tumor drains. A blue dye such as
patent blue-V or isosulfan blue is injected into a primary tumor which travels to the
5 lymph nodes and identifies the sentinel node. In some cases, there may be more than one
sentinel. . .

0 Texaphyrins possess inherent biolocalization specificity for lipid-rich tissue, such
as tumor, for example, as demonstrated in U.S. patents to texaphyrins cited herein and as
demonstrated in Example 1. Biolocalization specificity means having. .

.
. . .
nitro, formyl, acyl, hydroxyalkyl, alkoxy, hydroxyalkoxy,
hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy, carboxyalkyl,
carboxyamide,
carboxyamideAcyl, amino, aminoaflql, a site-directing molecule, a
catalytic group, or a
couple that is coupled to a site-directing molecule
or to a catalytic group.
. . .
R,5 and RIO,-.R,7 are independently hydrogen, A-yl, alkenyl, alkynyl,
aryl,
hydroxyAyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl,
carboxyAcyl,
carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or a couple
that is coupled to a
saccharide, to a catalytic group, or to a site-directing molecule; and n
is an integer value less
0 than or. . .

In one embodimen't of the present invention, a texaphyrin is further
coupled to a
site-directing molecule to form a conjugate for targeted in
vivo delivery. Site-directing
means having specificity for targeted sites. Specificity for targeted
sites means that
upon contacting the texaphyrin-conjugate with the targeted
site, for example, under
physiological conditions of ionic strength, temperature, pH and the
like, specific binding
1 0 will occur. The interaction may occur due to specific electrostatic,
hydrophobic, or
other interaction of certain residues of the conjugatewith
specific residues of the target
to form a stable complex under conditions effective to promote the
interaction.
. . .
include
but are not limited to: polydeoxyribonucleotides,
oligodeoxyribonucleotides, polyamides
1 5 including peptides having affinity for a biological receptor and
proteins such as
antibodies; steroids and steroid derivatives; hormones such as
estradiol, or histamine;
hormone mimics such as morphine; and further macrocycles such as
sapphyrins and
rubyrins. A preferred site-directing molecule is a melanocyte-directed
molecule, such as
an antibody having binding specificity for a
melanocyte-associated protein, for example,
2 0 tyrosinase (an important enzyme in melanin synthesis),
tyrosinase-related protein- I
(TRP- 1, gp75), or gp I 00 (Chen et al., 1995). Monoclonal
antibody T31 I is an example
of an antibody having binding specificity for tyrosinase (Chen
et al., 1995), and antibody
HMB45 is an example of an antibody having binding specificity
for an epitope specific
for melanocytes, malignant melanomas and melanoma metastases
(Schwichheimer and
2 5 Zhou, 1995). An exemplary. . .
. . .
the 6-catbon ring
of benzene or the condensed 6-carbon rings of the other aromatic

derivatives. For example,
an aryl group may be phenyl or naphthyl, and the term as used
herein includes both
unsubstituted aryls and aryls substituted with one or more nitro,
carboxy, sulfonic acid,
hydroxy, oxyalkyl or halide substituents. In this case, the substituent
on the phenyl or
0 naphthyl may be added in a synthetic step after the condensation step
which forms the
macrocycle.

Representative examples of oxyalkyls include the alkyl groups as herein
described
having ether linkages. 'Oxyalkyl is meant to include
polyethers with one or more functional
groups. The number of repeating oxyalkyls within a substituent may. .
. - I 00, preferably I - I 0, and more preferably, 1
Oxyhydroxyalkyl means alkyl groups having ether or ester
linkages, hydroxyl
groups, substituted hydroxyl groups, carboxyl groups, substituted
carboxyl groups or the
like.

Carboxymnideakl means alkyl groups with secondary or tertiary arnide
linkages
or the like. Carboxyalkyl means alkyl groups having hydroxyl groups,
carboxyl or amide
substituted ethers, ester linkages, tertiary amide
linkages removed from the ether or the Eke.
. . .
and
the like, derivatives thereof, and texaphyrin metal complexes. The
catalytic group is attached
either directly to the texaphyrin or via a linker or
couple of variable length.

A couple may be described as a linker, i.e., the
covalent product formed by reaction
of a reactive group designed to attach covalently another molecule at a
distance from the
texaphyrin macrocycle. Exemplary finkers or couples are
amides, amine, disulfide, thioether,
ether, ester, or phosphate covalent bonds.

In most preferred embodiments, conjugates and appended groups
are covalently
5 bonded to the texaphyrin via a carbon-carbon, carbon-nitrogen,
carbon-sulfur, or a carbon-
oxygen bond, more preferably. . .
. . .
iodide. Other preferred functionafizations are where R6 and R9 are
hydrogen, then R5, Rio, RI I and R12 are independently hydrogen,
phenyl, lower alkyl or
lower hydroxyalkyl. The lower alkyl is preferably methyl or ethyl, more
preferably methyl.

The lower hydroxyalkyl is preferably of I to 6 carbons and I to 4
hydroxy groups, more
preferably 3-hydroxypropyl. The phenyl may be substituted or
unsubstituted. In a
5 presently preferred texaphyrin I or H, RI is (CH2)2CH20H, R2 and R3
are CHXH3, R4 is
CH3, % is a site-directing molecule or a couple that is
coupled to a site-directing

molecule, and R7 is H or OCH3. A couple that is
coupled to a site-directing molecule
may be further described. as O(CH2CH20).- where m is I - I 0 and
preferably 1-5, or. . . is (CH2)2CH20K R2
and R3 are CH2CH3, R4 is CH3, R7 is O(CH2CH20)2CH2CH20CH3, and 14 is a
site-
directing molecule or a couple that is coupled to a
site-directing molecule.
1 0 In a further presently preferred texaphyrin I or R RI is (CH2)]CH20K
R2 and
R3 are. . .
. . .
in TABLE A and for R-rR12 in TAI
TXP RIF RO Rg Rio
Al O(CH2)30H O(CH2)30H H H
A2 O(CH2CH20)3CH3 O(CH2CH20)3CH3 II to
A3 O(CH2)nCON-linker-SDM, if
n=1-10
A4 O(CH2),,CON-linker-SDM, H to
n=1-10
A5 OCH2CO-SDM to
A6 O(CH2CH20)3CH3 11
A7 OCH2CON-linker-SDM O(CH2CH20)3CH3
A8 OCH2CO-SDM it of of
A9 O(CH2CH20)100CH3 of it #I
AlO OCH2CON(CH2cH20H)2 H of
All CH2CON(CH3)CH2- to to of
(CHOH)4CH20H
A12 if to to it
A13. . . B - CONTINUED
TXP RIF Rs Rg Rto
A15 OCH3 OCH3 of it
A16 OCH2CO2-SDM H to
A17 O(CH2),,COOK n- 10 of of 14
A18 (CH2),,-CON-linker-SDM, of If of
n=1-10
A19 YCOCH2-linker-SDM, to It
Y=NKO
A20 O(CH2)2CH20H O(CH2)2CH20H to
A21 of It it
A22 OCH2COOH O(MCH20KH3 to
A23 O(CH2),,CO-SDM, n=1-10 H of it
A24 O(CH2CH20)3CH3 o(CH2CH20)n-linker-
SDM, n7 10
A25 OCH3 OCH2CO-SDM
A26 to CH2CO-SDM
A27 it it
A28 OCH3 CH2CO-SDM H H
A29 to OCH3 of
A30 of of
A31 H O(CH2),,COOK n=1-10 to
TABLE B - CONTINUED
TXP R7 Rs Rg Rio
A32 of (CH2),,-CON-linker-SDM,
n=1-10
A33 OCH3 O(CH2CH20)3-CH3
A34 to of
A35 H O(CH2),,CO-SDM, n= I - I 0
A36 OCH3
A37 O(CH2CH20)3CH3
A38 O(CH2CH20)n-SDM7 n--l-
10
A39 O(CH2)30H O(CH2)30H O(CH2)30H H
A40 O(CH2CH20)3CH3. . . publications incorporated by reference herein

could extend and refine the referenced basic synthetic chemistry to produce texaphyrins, having various substituents. For example, polyether-linked polyhydroxylated groups, saccharide substitutions in which the saccharide is appended via an acetal-like glycosidic linkage, an oligosaccharide or a polysaccharide may be similarly linked to a texaphyrin. A doubly carboxylated texaphyrin in which the carboxyl groups are linked to the texaphyrin core via aryl ethers or functionalized allcyl substituents could be converted to various esterified products wherein the ester linkages serve to append further hydroxyl-contdming 1 0 substituents. Polyhydroxylated texaphyrin derivatives may be synthesized via the use of secondary amide linkages. Saccharide moieties may be appended via amide bonds.

Polyhydroxylated texaphyrin derivatives containing branched polyhydroxyl (polyol) subunits may be appended to the texaphyrin core via aryl ethers or ester linkages.

Treatment of carboxylated texaphyrins with thionyl chloride orp-nitrophenol acetate 1 5 would generate activated acyl species suitable for attachment to monoclonal antibodies or other bioniolecules of interest. Standard in situ coupling methods (e.g., 1, F-carbonyidiirnidazole) could be used to effect the conjugation.

. . .

detergent dialysis, for example. Preparation may be carried out in a solution, such as a phosphate buffer solution, containing texaphyrin-lipophilic 0 molecule conjugates so that the conjugate is incorporated into the liposome membrane.

Alternatively, the conjugate may be added in already formed liposomes. Liposomes employed in the present invention may be of any one of a variety. . .

In the following examples, PDT of the highly pigmented and metastatic B 16 melanoma using LuT2BET resulted in significant tumor retardation and increased 0 longevity of the treated animals. Without being bound by theory, the increased PDT responsiveness of the melanoma may be attributed to the high tumor loading achieved by the texaphyrin in addition to enhanced tissue penetration attained by illumination of the tumor with 732 nm light.

The right flanks of the mice were shaved and depiled the day prior to tumor inoculation.

B 16F IO cells (5 x105 cells in 0.05 mL PBS) were injected subcutaneously into the right hind flanks. Tumor size, i.e., length (1), width (w), and height (h), was measured 3 times a week with a vernier caliper. Tumor volumes were calculated using the formula for a herniellipsoid (Rockwell and Kaman, 1972).

V = x/6 x 0) x (w) x (h)
Biodistribution studies were performed on tumors having surface diameters of between about 5 7 mm and a depth of 4-6 mm.

Table C. Biodistribution of LuT2BET in B16 melanoma-bearing mice

LuT2BET (pmol/kg)	Time (h)	Plasma	Tumor	Muscle	Liver	Skin
0	0	0	0	0	0.3±0.4	0
10	3	8.9±1.0	11.3±3.7	1.3+0.4	94.5±11.6	5.9±1.3
10	5	1.2±0.2	11.4+1.1	0.8±0.2	61.9±8.3.	. .

Tumor levels of the texaphyrin were higher than plasma, muscle and skin at all three time points. The 20 pmol/kg dose produced greater tissue concentrations compared to the 10 gmol/kg dose, with the exception of the tumor levels at 24 h.

I 0 The texaphyrin exhibited good tumor localizing capacity as shown in Table C.

The tumor:muscle ratios, for the lOpmol/kg dose, were 8.6:1, 15: 1, and 10. 1: I for 3 h, 5 h, and 24 h. . . 5 -3 to 1. I-Egh concentrations 5 were found in the liver, showing that the texaphyrin is not exclusively retained by the tumor. However, no toxicity was observed in this study.

. . .
values of 5.1 pg/g, 4.7 pg/g, and 2.8 Ag/g at 0 3 h, 5 h, and 24 h after injection, yielding tumor:muscle ratios of 8.45: 1, IO: I and 7: 1, respectively. Therefore, increased uptake of lutetium texaphyrin into B 16 melanoma was observed. . .

. . .
the B 16 melanoma 5 h after administration of IO pmol/kg or 20 pmol/kg LuT2BET produced significant retardation of growth of the tumor; in some cases the longevity of the animals was doubled. PDT response was dependent upon drug dose, irradiation exposure and administration time.

0 PDTProlocol: C57 mice, bearing 13161710 melanoma as described in Example 1, were used for PDT experiments when the tumors reached surface diameters of between 4-6 mm and a depth of 2 3 mm. The mice were injected intravenously with LuT2BET (IO. . . 732 nm using a LAM33DA PLUSO argon pumped dye laser (Coherent, Palo Alto, 5 CA). A 400 gm diameter fiberoptic cable coupled the laser to a microlens which produced uniform light intensity in the treatment field. Light fluences ranged between 150 and 600 j/CM2. . .

0 Tumor Temperature Measurements: Tumor temperature during laser irradiation was monitored with a 33 gauge hypodermic thermocouple probe (Omega Engineering,

Stamford, CT) placed percutaneously at the base of the tumor.

Results of PDT with LuT2BET in B 16F IO melanotic tumors are shown in
Tables D and E. No measurable increase in tumor temperature was observed during the
5 course of PDT treatment using light fluences between 150 to 600 j/CM2 at 15OMW/CM2
thereby ruling. . .

2Time to reach ten times the original tumor volume (mean ± SD).

No significant difference in tumor regrowth was seen when comparing normal
tumors, those irradiated with 400 J/cm2, and those treated with sensitizer alone. A
significant response was seen when the tumors were irradiated 5 h after sensitizer
administration(P<0.001). Thetimeforthetumorstoregrow(totentimestheir original volume) was increased to 15.3 days with a light fluence of 300 j/CM2. . . group. Irradiation 24 h after photosensitizer injection with a
light fluence of 150 j/CM2 did not yield any significant change in tumor regrowth when
compared to controls, however an increase in light fluence to 3OOj/CM2 increased the
time for tumor regrowth to 9.6 days (P = 0.002) compared to controls.

2Time to reach ten times the original tumor volume (mean ± SD).

. . .

Table E. Following an intravenous injection of 10 pmol/kg and a light fluence of 3 OOj/CM2 , no detectable inhibition of tumor
regrowth was seen. However, light doses of 400, 500 and 600 j/CM2 Si gnificantly
increased the PDT effect of LuT2BET at 10 pmol/kg. At a 600 J/cm2 light dose, the
tumors grew to I OX their initial tumor volume in 15.6 days, compared to 5.9 days for
untreated controls (P < 0.0001).

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CLMEN. . . hydroxyAyl, alkoxy,

hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy, carboxyAyl, carboxyarride, carboxyarridealkyl, amino, aminoalkyl, a site-
3 0 directing molecule, a catalytic group, or a couple that is coupled to a site-
directing molecule or to a catalytic group;
R6 and R9 are independently selected from the groups of RI-R] R7. . . other than
iodoalkyl;
R5 and R,rRu are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, hydroxyAyl, alkoxy, hydroxyalkoxy, hydro)tyalkenyl, hydroxyalkynyl, carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoAryl, or a couple that is coupled to a saccharide, to a
catalytic group, or to a site.
directing molecule; and
n is an integer value less than or. . . hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy,
3 0 carboxyalkyl, carbo3qmmide, carboxyamidealkyl, amino, aminoalkyl, a site.
directing molecule, a catalytic group, or a couple that is coupled to a site-
directing molecule or to a catalytic group;
R6 and R9 are independently selected from the groups of RI -R4,. . . other than
iodoalkyl;
Rs and RIvRI2 are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, carboxyalkyl, carboxyamide, carboxyamidealiql, amino, aminoalkyl, or a couple that is coupled to a saccharide, to a
catalytic group, or to a site-
directing molecule; and
R13 is alkyl, alkenyl, oxyalkyl, or hydroxyalk-yl having. . .

8 The use of claim 7 wherein the melanodermic lesion is a neoplasm or a malignant
lesion.
5 9. The use of claim 8 wherein the malignant lesion is melanoma.

14 The use of claim 2 or 3 wherein the site-directing molecule is an antibody having
binding specificity for tyrosinase.

. . .
wherein the pigmented lesion is a
melanodermic lesion.
I 0 25. The method of claim 24 wherein the melanodermic lesion is a neoplasm or a
malignant lesion.

. . .
fonnyl, acyl, hydroxyalkyl, alkoxy,
hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy,
carboxyalky], carboxyarnide, carboxyamidealkyl, amino, aminoalkyL a site-
directing molecule, a catalytic group, or a couple that is coupled to a site-
directing molecule or to a catalytic group;
2 5 R6and R9 are independently selected from the groups of RI-R4,. . . than
iodoalkyl;
R5 and Rio-R12are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, hydroxyal4l, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl,
3 0 carboxyalkyl, carboxyamide, carboxyamideA-yl, amino, arninoalkyl, or a
couple that is coupled to a saccharide, to a
catalytic group or to a site.

directing molecule; and
n is an integer value less than or. . .
. . .
hydroxyalkyl, alkoxy,
2 0 hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl, saccharide, carboxy,
carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, a
site-
directing molecule, a catalytic group, or a couple that is
coupled to a site-
directing molecule or to a catalytic group;
R6 and R9 are independently selected from the groups of RI-R4, R7. . .
and RIO-RI2 are independently hydrogen, allcyl, alkenyl, alkynyl, aryl,
hydroxyalkyl, alkoxy, hydroxyalkoxy, hydroxyalkenyl, hydroxyalkynyl,
carboxyalkyl, carboxyamide, carboxyamidealkyl, amino, aminoalkyl, or a
3 0 couple that is coupled to a saccharide, to a
catalytic group, or to a site-
directing molecule; and
R13is alkyl, alkenyl, onalkyl, or hydroxyalkyl having up. . .
. . .
Lu(M), La(HI), In(RD, Y(IM, Dy(M), Zn(H)
or Cd(III).
2 0 A The method of claim 30 wherein the site-directing molecule is an
antibody having
binding specificity for tyrosinase.

39 The method of claim 31 wherein the site-directing molecule is an
antibody having
binding specificity for tyrosinase.
2 5

=> d kwic 3

L31 ANSWER 3 OF 4 PCTFULL COPYRIGHT 2006 Univentio on STN
ABEN . . . hydrolysis.
These texaphyrin metal complexes having enhanced stability are useful
for localization, magnetic
resonance imaging, radiosensitization, radiation therapy, fluorescence
imaging, photodynamic tumor
therapy and applications requiring singlet oxygen production for
cytotoxicity. Electron withdrawing
groups at positions 15 or 18 render the macrocycle. . .

DETD Texaphyrin refers to an expanded porphyrin pentadentate
macrocyclic ligand. The compound is capable of existing
in both its free-base form and of supporting the
formation of a 1:1 complex. . .

Large, or expanded porphyrin-like systems are of
interest for several reasons: They could serve as
aromatic analogues of the better studied porphyrins or
serve as biomimetic models. . . versatile ligand!] capable
of,binding larger metal cations and/or stabilizing higher
coordination geometries than those routinely accommodated
within the normally tetradentate ca. 2.0 A radius
porphyrin core. The resulting complexes could have
important application in the area of heavy metal
chelation therapy, serve as contrast agents for magnetic
resonance. . .

The water-soluble porphyrin derivatives, such as
tetrakis(4-sulfonatophenyl)porphyrin (TPPS) cannot
accommodate completely the large gadolinium(III) cation
within the relatively small porphyrin binding core (r

2.0 A), and, as a consequence, gadolinium porphyrin complexes are invariably hydrolytically unstable.

9
while porphyrin derivatives have high triplet yields and long triplet lifetimes (and consequently transfer excitation energy efficiently to triplet oxygen), their absorption in the Q-band. . .

Hematoporphyrin derivative and Photofrin IIO (oligomeric hematoporphyrin derivative) act as efficient photosensitizers for the photo-deactivation of cell-free HIV-1, herpes simplex (HSV), hepatitis and other enveloped viruses in far lower dosages than are required for tumor treatment. The success of this procedure derives from the fact that these dyes localize selectively at or near the morphologically characteristic, and physiologically. . .

(1972) there appear to be only three large porphyrin-like systems which might have utility as photosensitizers.
. . .
CHC1 3 is 10-fold
more intense and red shifted by almost 200 nm as compared to that of a typical reference cadmium(II) porphyrin.
. . .
60 and 70%
2
when irradiated at 354 nm in air-saturated methanol, (Harriman et al. 1989). Related congeneric texaphyrin systems bearing substituents on the tripyrrole-and/or phenyl portions and incorporating La(III) and/or Lu(III) metal centers have been found to produce lo 2 in quantum yields exceeding 70% when irradiated. . .
. . .
R7 and R8 are independently hydrogen, halide, hydroxyl, alkyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxy, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule.

R. and R10-R12 are independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to a saccharide, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule. For this embodiment, at least one of RS: R6-. . .

In this case, RI-R4 and R6-R9 are independently hydrogen, hydroxyl, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological is receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule. R. and RiCR12 are independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to a

saccharide, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule. At least one of R51 R60' R.91 Rio-,. . . . . .
R7 and R8 are independently hydrogen, halide, hydroxyl, alkyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxy, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule. R. and Rio]R' are
12
independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to a saccharide, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule. R6 and R. are independently hydrogen, halide other than. . .

A couple may be an amide, thiol, thioether, or ether covalent bond. An oligonucleotide, an antibody, a hormone or a sapphyrin may have binding specificity for localization to a treatment site.

- 10 -

Preferred substituents for R6 include carboxy, alkyl or carboxyamidealkyl having a tertiary amide linkage.

The use of a texaphyrin diamagnetic-metal complex having a substituent at the 2, 71 12, 15, 18 and/or 21 position and an. . . using said texaphyrin to form long-lived triplet states in high yield; and iv) a method of treating a host harboring atheroma or neoplastic tissue comprising administering to the host an effective amount of said texaphyrin complex, the complex exhibiting selective biolocalization in the atheroma or neoplastic tissue relative to surrounding tissues, and photoirradiating the texaphyrin complex in proximity to the atheroma or neoplastic tissue. .

Further aspects of the present invention include the use of a texaphyrin paramagnetic-metal complex having a substituent at the 2, 71 12,. . . a subject an effective amount of said texaphyrin followed by MR imaging of the subject; iii) a method of detection of atheroma or neoplastic tissue in a subject comprising administering to the subject said texaphyrin in an amount effective to enhance a magnetic resonance image and detecting the atheroma or neoplastic tissue by MR imaging of said subject; iv) a method of imaging an organ in a subject comprising administering to the subject. . .

A method of treating a host harboring atheroma or neoplastic tissue is also an aspect of the present invention, such method comprising administering to the host as a first agent a texaphyrin detectable-metal complex of the present invention, said complex exhibiting selective biolocalization in the atheroma or neoplastic tissue relative to surrounding tissue; determining localization sites in the host by reference to such texaphyrin-detectable metal complex; administering to the

host as a. . . and exhibiting the ability to generate singlet oxygen upon exposure to light; and photoirradiating the second agent in proximity to said atheroma or neoplastic tissue.

The present invention provides a method of radiation therapy for a host harboring atheroma or neoplastic tissue, the method comprising administering to the host a texaphyrin of the present invention, and administering ionizing radiation to the host in proximity to the atheroma or neoplastic tissue. The radiation may be administered either before or after administration of the texaphyrin. The texaphyrin exhibits greater biolocalization in the atheroma or neoplastic tissue relative to surrounding tissues and has radiosensitization properties. An additional step may be included, the step being the determination of localization sites of the atheroma or neoplastic tissue in the host by monitoring texaphyrin concentrations.

one skilled in the art would recognize in light of the present disclosure that sapphyrin-conjugated texaphyrin metal complexes may be used in methods for generating singlet oxygen. Sapphyrins compounds are disclosed in U.S. Patents 5,159,065 and 5,120,411 which are. . .

. . .
R7 and R8 are independently hydrogen, halide, hydroxyl, alkyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxy, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule.

R.5j' Rior R11 and R12 are independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to a saccharide, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule; and at least one of Rs, R61 R.9j,. . .

. . .
the present invention, the halide other than iodide may be fluoride, chloride or bromide. The alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxyalkyl, carboxyamidealkyl, oligonucleotide, antibody, hormone, peptide, or sapphyrin, or molecule couple is covalently bonded to the texaphyrin via a carbon-carbon, a carbon-nitrogen or a carbon-oxygen bond. The aryl may be a phenyl group, unsubstituted or substituted with a nitro, carboxy, sulfonic acid, hydroxy, oxyalkyl or halide other than iodide substituent. In this case, the substituent on the phenyl group may be added in a synthetic step after the condensation step which forms the madrocycle.

Representative examples of oxyalkyls include the alkyl groups as herein described having ether linkages.

Hydroxyalkyl means alkyl groups having hydroxyl groups attached. Oxyalkyl means alkyl groups attached to

an oxygen. Oxyhydroxyalkyl means alkyl groups having ether or ester linkages, hydroxyl groups, substituted hydroxyl groups, carboxyl groups, substituted carboxyl groups or the like. Saccharide includes oxidized reduced or substituted saccharide; hexoses such as D-glucose,. . .

. . .

sugars are galactosamine, glucosamine, sialic acid and D-glucamine derivatives such as 1-amino-l-deoxysorbitol. Carboxyamidealkyl'means

alkyl groups with hydroxyl groups, secondary or tertiary amide linkages or the like. Carboxyalkyl means alkyl groups having hydroxyl groups, carboxyl or amide substituted ethers, ester linkages, tertiary amide linkages removed from the ether or the like.

Carboxyamidealkyl may be alkyl having secondary or a a tertiary amide linkages or (CH2)nCONHR I O(CH2)nCONHR I (CH2) nCON (Ra 2, or 0 (CH2) nCON (Ra)2 where n is a positive integer from. . .

A couple may be described as a linker, i.e., a reactive group for attaching another molecule at a distance from the texaphyrin macrocycle. An exemplary linker or couple is an amide, thiol, thioether or ether covalent bond as described in the examples for attachment of oligonucleotides and antibodies.

For the above-described texaphyrins, the couple may be an amide, thiol, thioether or ether covalent bond,the oligonucleotide, the antibody, the hormone or the sapphyrin may have binding specificity for localization to a treatment site and the biological receptor may be localized to. . .

. . .

aromatic w system. Such electron donating groups include hydroxyl, alkyl, haloalkyl other than iodoalkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to any of these molecules. Hydrolysis-resistant texaphyrin metal complexes are useful for localization, magnetic resonance imaging, radiosensitization, radiation therapy, fluorescence imaging, photodynamic tumor therapy and applications requiring singlet oxygen production for cytotoxicity.

. . .

of a gadolinium(III) metallotexaphyrin complex. U.S. Patent 5,252,720 describes photosensitized inactivation of enveloped viruses and magnetic resonance imaging (MRI) of atheroma, liver, kidney and tumor using various substituted texaphyrin metal complexes. Altering the polarity and electrical charges of side groups of the texaphyrin macrocycles alters the degree, rate,. . .

Powerful techniques include the use of these texaphyrins in magnetic resonance imaging followed by photodynamic tumor therapy in the treatment of atheroma, and benign

and malignant tumors or followed by sensitized X-ray treatment.

. . .

method of magnetic resonance image enhancement comprising administering to a subject an effective amount of said texaphyrin; iii) a method of detection of neoplastic tissue in a patient comprising the steps of administering to a patient said texaphyrin in an amount effective to enhance a magnetic resonance image and detecting neoplastic tissue by magnetic resonance imaging of said patient; iv) a method of imaging an organ in a patient comprising administering to a patient. . .

- 27

A method of treating a host harboring atheroma or benign or malignant tumor cells is also an aspect of the invention. An exemplary preferred method includes administering to the host as a first agent a. . . having a substituent at the 2,
71 12, 15, 18 or 21 position, said complex exhibiting selective biolocalization in such atheroma or tumor cells relative to surrounding tissue; determining localization sites in the host by reference to such detectable metal; administering to the host as a. . . and exhibiting the ability to generate singlet oxygen upon exposure to light; and photoirradiating the second agent in proximity to said atheroma or tumor cells.

A method of treating a host harboring tumor cells comprises the steps of: i) administering to the host an effective amount of a texaphyrin diamagnetic-metal complex having a substituent at the 2, 71 12, 15, 18 or 21 position, the complex exhibiting selective biolocalization in the tumor'cells relative to surrounding tissue; and ii) photoirradiating the texaphyrin-diamagnetic metal complex in proximity to the tumor cells. The photoirradiating is generally at a wavelength of about 730 to 770 nanometers or may be from laser light. In these. . .

The present invention provides a method of radiation therapy for a host harboring a tumor. The method includes the steps of administering to the host a texaphyrin having a substituent in the 2, 71 12, 15, 18 and/or 21 position(s), and administering ionizing radiation to the host in proximity to the tumor either before or after administration of the texaphyrin. The texaphyrin exhibits greater biolocalization in the tumor relative to non-tumor tissue and has radiosensitization

- 29

properties. A tumor may be a benign or malignant tumor or may be atheroma. A texaphyrin having radiosensitization properties enhances cytotoxicity from ionizing radiation as compared to control experiments without the texaphyrin. Ionizing radiation. . .

An improved method of treating a host harboring a tumor comprises the further step of determining localization sites in the host by monitoring texaphyrin concentrations. The texaphyrin may be complexed with a metal,. . .

A further improved method of treating a host

harboring a tumor comprises the additional steps of administering to the host as a second agent a texaphyrin-diamagnetic metal complex having a substituent at. . . 2, 71 12, 15, 18 or 21 position and having essentially identical biolocalization property and administering ionizing radiation and photoirradiation in proximity to the tumor.

Exhibiting greater biolocalization in the tumor relative to non-tumor tissue means having an inherently greater affinity for tumor tissue relative to non-tumor
tissue. The second agent has essentially identical biolocalization property as the first agent and exhibits the ability to generate singlet oxygen upon exposure. . .

A preferred embodiment of the present invention is a method of radiation therapy for a host harboring a tumor comprising the steps of i) administering to the host a pharmaceutically effective amount of the Gd complex of a texaphyrin having a substituent. . . at the 2, 71 12, 15, 18 and/or 21 position(s); and ii) administering ionizing radiation to the host in proximity to the tumor, either before or after administration of the texaphyrin metal complex.

. . .
21 position(s) of the macrocycle. Examples 7-13 describe the use of texaphyrins of the present invention for imaging, radiosensitization, radiation therapy and photodynamic tumor therapy.

. . .
example, RI is 3-hydroxypropyl, R2 and R3 are ethyl and R4 is methyl. The tripyrrane portion of the molecule is important for linking the macrocycle to biologically important molecules such as an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule and the like.

Such macrocycles can be further functionalized to derivatives having an antibody, oligonucleotide, protein, peptide, sapphyrin and the like on one position of the B portion of the molecule.

. . .
or iodide in the presence of a Lewis acid such as AlC13, for example. The 3 and 6 positions of the phenyl ring are derivatized with the alkyl group to form compound A2. A mixture of reactants having a single halide and different alkyl groups. . .

Ortho-phenylenediamine compounds having substituents bound to the phenyl ring via an oxygen are prepared as indicated in Schemes B and C.

. . .
2,3,4-
trihydroxybenzoic acid (M). Compound D3 (B3) is treated with an amine component in 1,3-dicyclohexylcarbodiimide and dimethylformamide to form D4 having an amide linkage.

Alternative coupling reagents include 1,11-carbonyldiimidazole (CDI) or ECC. Reduction as described above yields the diamine for condensation with a tripyrrane ketone.

. . .

to react with these new
functionalized tripyrranes. The organic synthesis
required for the various transformations illustrated in
Scheme I is derived from classic pyrrole/porphyrin
chemistry.

. . .

halide other than iodide, hydroxyl, alkyl, aryl,
haloalkyl other than iodoalkyl, nitro, formyl, acyl,
hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide,
carboxy, carboxyalkyl, carboxyamidealkyl, an
oligonucleotide, an antibody, a hormone, a peptide having
affinity for a biological receptor, a sapphyrin molecule,
or a couple to an oligonucleotide, an antibody, a
hormone, a peptide having affinity for a biological
receptor or a sapphyrin molecule.

Groups on Rs or RIO may be alkyl, aryl,
hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl,
carboxyamidealkyl or a couple to a saccharide, an
oligonucleotide, an antibody, a hormone, a peptide having
affinity for a biological receptor or a sapphyrin
molecule, for example.

Electron donating substituents may be hydroxyl,
alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl,
saccharide, carboxyalkyl, carboxyamidealkyl, an
oligonucleotide, an antibody, a hormone, a peptide having
affinity for a biological receptor, a sapphyrin molecule,
or a couple to an oligonucleotide, an antibody, a
hormone, a peptide having affinity for a biological
receptor or a sapphyrin molecule.

. . .

the macrocycle by reacting 1,2-dialkyl-4,5-
dinitrobenzene with bromine in the presence of FeBr3 or
AlBr3. The 3 and 6 positions of the phenyl ring are
derivatized with bromide and reduction to the amine as
described in example 2 prepares the precursor for
condensation with a diformyltripyrrole. . .

. . .

R9 Ric R11
Al O(CH2)30H O(CH2)30H O(CH2)30H H H
A2 O(CH2cH20)3CH3 O(CH2cH20)3CH3 COOH
A3 002CH20) O(CH2cH20)3CH3 0-saccharide
A4 if 11 O(CH2cH20)3CH3
A5 0026CON-finker-oligo
A6 H OCH CON-linker-oligo OCH
2 3
A7 OCH CO-poly-Hysine
2
AB OCH CO-estradiol
2
A9 O(CH2cH20)3CH3
AlO O(CH2cH20)3CH3 to
All OCH CON-linker-oligo
2
A12 OCH CO-estradiol
2
A13 O(CH2cH20)3CH3 O(CH2cH20)3CH3
OCH CO-estradiol
2
Table B. continued...

. . .

OCH3
A16 H saccharide

A17 O(CH2)3OH O(CH2)3OH H CH3
A18 H O(CH CH 0)3CH3 it IF
2 2
A19 O(CH2CH2O)3CH3 go of to
A20 H OCH CON-linker-oligo H CH
2 3
A21 OCH CO-estradiol
2
A22 OCH2CON(CH2CH2OH)2
A23 O(CH2CH2O)3CH3 O(CH2CH2O)12
A24 of OCH CON-linker-oligo
2
A25 H CH2CON(CH3)CH2.
. . .
OCH
3
A38 H OCH2C02-glucosamme CH2(CH2)60H
A39 O(CH2)30H O(CH2)30H H CH3 CH3
or or
I CH2CH3 CH2CH3
A40 O(CH2CH20)3CH O(CH2CH20)3CH3
A41 O(CH2)30H O(CH CH 0)3CH3
2 2
A42 H o(CH2)nCON-linker-oligo,
n=1,2,3
A43 H O(C2),CO-estradiol,
n=1,2,3
A44 H saccharide
Table B. continued...

TXP R7 RO R9 Rip R11
A45 O(CH2)30H O(C2),CON-linker-oligo,
n=1,2,3
A46 O(CHACO-estradiol,
n=1,2,3
A47 saccharide
A48 O(CH2CH20)3CH3 O(CHACON-linker-oligo,
n=1,2,3
A49 of O(CH2)nCO-estradiol,
n=1,2,3
A50 saccharide
A51 O(CH2)nCON-linker-oligo H
n=1,2,3
A52 O(CH CH 0)3CH3
2 2
A53 CH (CH 1
2 2 2
A54 O(CH2)nCON-linker-oligo
n=1,2,3
A55 CH or
3
,CH2CH3
A56 O(CH CH 0) CH
2 2 3 3

A substituent on the R., R R or R
101 11. . . may be derivatized after condensation of the macrocycle. Substituents may include an alkyl group having up to 5 carbon atoms or a phenyl group which may be further derivatized with a nitro, carboxyl, sulfonic acid, hydroxyl, halide or alkoxy where the alkyl of the alkoxy may. . .
. . .
08/135,118 so

as to produce texaphyrins having various substituents, yet having basic utility to those specifically detailed in the present examples. For example, polyether-linked polyhydroxylated groups, catechol (i.e. benzene diol) derivatives bearing further hydroxyalkyl substituents off the tripyrrane-derived portion of the macrocycle, saccharide substitutions in which the saccharide is appended via an acetal-like glycosidic linkage, an oligosaccharide or a polysaccharide may be similarly linked to a texaphyrin. A doubly carboxylated texaphyrin in which the carboxyl groups are linked to the texaphyrin core via aryl ethers or functionalized alkyl substituents could be converted to various esterified products wherein the ester linkages serve to append further hydroxyl-containing substituents. Polyhydroxylated texaphyrin derivatives may be synthesized via the use of secondary amide linkages. Saccharide moieties may be appended via amide bonds. Polyhydroxylated texaphyrin derivatives containing branched polyhydroxyl (polyol) subunits may be appended to the texaphyrin core via aryl ethers or ester linkages.

- 70 -

Treatment of carboxylated texaphyrins with thionyl chloride or p-nitrophenol acetate would generate activated acyl species suitable for attachment to monoclonal antibodies or other biomolecules of interest.

Standard in situ coupling methods (e.g. 1,11-carbonyldiimidazole (CDI)) could be used to effect the conjugation.

The selectivity of the texaphyrins may be enhanced by covalently linking oligonucleotides onto the periphery of the macrocycle. Amides, ethers and thioethers are representative of linkages which may be used for this purpose. Oligonucleotides functionalized with amines at the 51-end, the 31-end, or internally at sugar or base residues. . . or thiol groups may be selectively alkylated at the sulfur atom(s) with an alkyl halide derivative of the texaphyrin complex. The resultant oligodeoxynucleotide-complex conjugates may be designed so as to provide optimal catalytic interaction between a target nucleic acid and the bound texaphyrin.

Another means of gaining selectivity may be to covalently link the texaphyrin complex to a sapphyrin (sap) molecule, (U.S. Patent 5,159,065; U.S. Patent 51120,411; U.S. Patent 5,041,078, all incorporated by reference herein.) Since sapphyrins bind DNA, K - 106 M-1, (USSN 07/964,607, incorporated by reference herein) the linked texaphyrin-sapphyrin complex (txph-sap) could effectively increase the texaphyrin concentration at locations adjacent to the sapphyrin binding sites.

. . .

system may be employed where the molecules are optimized to the laser wavelength; an excited sapphyrin ,may transfer its energy to the conjugated texaphyrin for detection. The texaphyrin molecule may further be designed to pass through cell membranes for selective radiosensitization.

. . .

derivatives in question. For instance, the texaphyrin complexes of choice may be administered in

- 73 -
varying concentrations to a variety of cancerous cells and the rate of cell replication determined both in the presence and absence of light. Similarly, texaphyrin complexes of choice may be. . .

EXAMPLE 8
Antibody Directed and Intrinsic Biolocalization
U.S. Patent 5,252,720 teaches using a texaphyrin bifunctional conjugate for use in radioisotope-based diagnostics and in radioisotope-based therapy. The
- 75 -
texaphyrin molecules of the present invention are especially suited for acting as bifunctional chelating agents in antibody conjugate-based treatment since they
have greater hydrolytic stability compared to the compounds of previous patent applications, they have functional groups suitable for conjugation to the antibody, they form covalent linkages that are stable in
vivo which do not destroy the immunological competence of the antibody, they are relatively nontoxic, and they are readily soluble in a physiological environment. A further advantage of these texaphyrins is that they. . .

The ability to attach and deliver a potent photosensitizer directly to a tumor locus could have tremendous potential benefit in the treatment of neoplastic disorders. In addition, this approach will allow a variety of useful radioisotopes such as 90 Y and ill In to be attached to a monoclonal antibody for specific targeting.

The texaphyrin molecules of the present invention are also suited f or delivering radioactivity to a tumor on their own since they chelate radioisotopes and have intrinsic biolocalization selectivity.

EXAMPLE 9
Texaphyrins as an Internal Radioactive Source
Radioisotopes play a central role in the detection and treatment of neoplastic disorders. Improving their efficacy in medical applications involves attaching radioisotopes to tumor-directed molecules. For example, radiolabeled antibodies could serve as magic bullets and allow the direct transport of radioisotopes to neoplastic sites thus minimizing whole body exposure to radiation. The use of bifunctional metal chelating agents in radioimmunodiagnostics (RID),
-
radiosensitization and therapy (RIT) is. . .
. . .
, and 'In (t,/2 = 67.4h) which
come closest to meeting these criteria. Each of these enjoys advantages and disadvantages with respect to antibody labeling for RID; these aspects are discussed in parent patent application 08/135,118. Texaphyrin forms a kinetically and hydrolytically stable complex with In3+ such a ligand system may be elaborated and serve as the critical core of a bifunctional conjugate for use in In-based radioimmunodiagnostics.
. . .
an emission energy of

2.28 MeV, it is calculated to deliver roughly 3 to 4 times more energy (dose) to the tumor per nanomole than either 186 Re or 67 Cu. A texaphyrin-type bifunctional conjugate may be prepared for use in 90 Y-based RIT. 90Y may be attached to an antibody of choice using a functionalized texaphyrin.

. . .

The Y3+ and In 3+ complexes of texaphyrin are formed rapidly (insertion and oxidation times are less than 3 hours) from the methylene-linked reduced precursor, and have a half-life of about 3 weeks in 1:1 methanol-water mixtures. 153 Gd is primarily a gamma emitter and. . . enhanced stability. A texaphyrin complexed to 90 Y may be administered in combination with another texaphyrin complexed to a diamagnetic metal for photodynamic tumor therapy, for example, to achieve a synergistic killing of malignant cells.

. . .

fibrosarcomas in their left flanks (n=4) were studied for imaging. Standardized signal intensities (SSI) increased in liver by 81.79*, kidney by 114.9%- and tumor by 49.7t from pre- to 10-15 minutes post-contrast.

These results show that the T2B2 gadolinium, complex of U.S. Patent 5,252,720 is an hepatic, renal and tumor-specific contrast agent. The agent was found to have relatively low toxicity in rodents. Tumor enhancement persisted for up to 28 hours.

. . .

and viable liver image augmentation was obtained when using doses as low as 2gmol/kg. Gd(IIVB2T2 was able to localize in hypoxic areas of tumors.

EXAMPLE 11
Radiation Sensitization of Tumor Cells
Using Gadolinium Texaphyrin
U.S. patent application USSN 08/135,118 teaches the use of texaphyrins as radiosensitizers to enhance the effect of radiation therapy.

. . .

relatively stable, yet reacts readily to covalently modify neighboring molecules, and
iii) texaphyrin may be particularly effective for treating the hypoxic areas of solid tumors because of intrinsic biolocalization and its indifference to the presence of 02.

. . .

12
Photodynamic Therapy
U.S. Patent 5,252,720 demonstrates results which show that La(III)B2T2 is phototoxic to murine mammary carcinoma cells in vitro and to murine adenocarcinoma tumor masses in Balb/c mice in vivo. Texaphyrins may be conjugated to biological molecules, especially proteins of molecular weight greater than about 20,000 daltons, e.g. albumin and gamma globulin, in order to slow their clearance by the kidneys. For photodynamic tumor therapy, a prolonged presence of these complexes in tissue may be desirable for photoirradiation purposes.

The conjugation would be accomplished as described in

Example 7 for antibody conjugates. U.S. Patent 5,252,720
also teaches the use of texaphyrins for localization by magnetic resonance imaging followed by photodynAmic therapy for treatment of a tumor.

- 82
The texaphyrins of the present invention, due to their greater hydrolytic stability, are especially appropriate candidates for localization by MRI, photodynamic tumor treatment and for the combined diagnosis and treatment discussed in U.S. Patent 51252,720.

EXAMPLE 13
Texaphyrins for Radiosensitization and Localization followed by Radiotherapy and/or Photodynamic Tumor Therapy for Tumor Destruction
This example describes the use of texaphyrins in the-localization, radiosensitization and destruction of tumor tissue. A texaphyrin is administered to a host harboring benign or malignant tumor cells. The texaphyrin exhibits radiosensitization properties and selective biolocalization in benign or malignant tumor cells relative to surrounding tissue. Localization sites in the host are determined by reference to the texaphyrin using-J, for example, magnetic resonance imaging. . . . . .
generate singlet oxygen upon exposure to light is administered. The second texaphyrin metal complex is photoirradiated in proximity to the benign or malignant tumor cells, as with fiber optics, to cause tumor tissue
destruction from the singlet oxygen produced. The metal in the second texaphyrin metal complex is a diamagnetic metal, preferably La(III), Lu(III) or. . .

Texaphyrin-metal complexes will be chosen which themselves show a high intrinsic biolocalization selectivity for tumors or neoplastic tissues. For example, texaphyrin complexes demonstrate in vivo affinity for tissue high in lipid content, atheroma, the liver, kidneys and tumors.

Texaphyrin complexes are good candidates for such biomedical radiosensitizers and photosensitizers. They soak up electrons in an irradiated area, allowing hydroxyl radicals to. . . damage, they are easily available, have low intrinsic cytotoxicity, long wavelength absorption, generate singlet oxygen, are soluble in physiological environments, have the'ability to be conjugated to site specific transport molecules,
- 84 -
have quick elimination, are stable and are easily subject to synthetic modification. Significant advantages to using. . .

CLMEN. . . U(III);
RI]N' R7 and R8 are independently hydrogen, halide, hydroxyl, alkyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxy, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a

peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, or a sapphyrin molecule;

- 86

R6 and R9 are independently selected from the. . . than iodide and the haloalkyl is other than iodoalkyl;

RS and R10-R12 are independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to saccharide, an oligonucleotide, an antibody, hormone, a peptide having affinity for a biological receptor, or a sapphyrin molecule;

at least one of RS, R61 R91 R10, R11. . .

. . .

The texaphyrin of claim 1 wherein:

Ri -R4 and R6-R. are independently hydrogen, hydroxyl, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, saccharide, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, or a sapphyrin molecule; and

RS and R10-R12 are independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to a saccharide, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, or a sapphyrin molecule.

. . .

R7 and RS are independently hydrogen, halide, hydroxyl, alkyl, aryl, haloalkyl, nitro, formyl, acyl, hydroxyalkyl, oxyalkyl,

- 87

oxyhydroxyalkyl, saccharide, carboxy, carboxyalkyl, carboxyamidealkyl, an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, a sapphyrin molecule, or a couple to an oligonucleotide, an antibody, a hormone, a peptide having affinity for a biological receptor, or a sapphyrin molecule;

R. and R10-R12 are independently hydrogen, alkyl, aryl, hydroxyalkyl, oxyalkyl, oxyhydroxyalkyl, carboxyalkyl, carboxyamidealkyl or a couple to saccharide, an oligonucleotide, an antibody, hormone, a peptide having affinity for a biological receptor or a sapphyrin molecule; and

R6 and R9 are independently halide other than iodide, formyl,. . .

4 The texaphyrin of claim 1, 2 or 3 wherein the couple is an amide, thiol, thioether or ether covalent bond.

5 The texaphyrin of claim 1, 2 or 3 wherein the oligonucleotide, the antibody, the hormone or the sapphyrin has binding specificity for localization to a treatment site.

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 NEWS  7  MAY 19  Derwent World Patents Index to be reloaded and enhanced
 NEWS  8  MAY 30  IPC 8 Rolled-up Core codes added to CA/CAplus and
                  USPATFULL/USPAT2
 NEWS  9  MAY 30  The F-Term thesaurus is now available in CA/CAplus
 NEWS 10  JUN 02  The first reclassification of IPC codes now complete in
                  INPADOC
 NEWS 11  JUN 26  TULSA/TULSA2 reloaded and enhanced with new search and
                  and display fields
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 NEWS 15  JUl 19  Coverage of Research Disclosure reinstated in DWPI
 NEWS 16  AUG 09  INSPEC enhanced with 1898-1968 archive

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               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.
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=> s 122341-38-2/rn
           296 122341-38-2
            21 122341-38-2D
L1         281 122341-38-2/RN
                 (122341-38-2 (NOTL) 122341-38-2D )

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       7824663 PY>1998
L2          91 L1 NOT PY>1998

=> s l2 and (cancer? or tumor? or neoplas?)
         302043 CANCER?
         437420 TUMOR?
         459043 NEOPLAS?
L3           71 L2 AND (CANCER? OR TUMOR? OR NEOPLAS?)
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=> s PDT or photodynamic
          3779 PDT
            32 PDTS
          3800 PDT
                 (PDT OR PDTS)
         13360 PHOTODYNAMIC
           474 PHOTODYNAMICS
         13676 PHOTODYNAMIC
                 (PHOTODYNAMIC OR PHOTODYNAMICS)
L4       14296 PDT OR PHOTODYNAMIC

=> s l4 and l3
L5          70 L4 AND L3

=> s antibod?
L6      468285 ANTIBOD?

=> s l6 and l5
L7           0 L6 AND L5

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           389 PDT/TI
             3 PDTS/TI
           392 PDT/TI
                 ((PDT OR PDTS)/TI)
          4875 PHOTODYNAMIC/TI
           167 PHOTODYNAMICS/TI
          5042 PHOTODYNAMIC/TI
                 ((PHOTODYNAMIC OR PHOTODYNAMICS)/TI)
L8        5339 (PDT/TI OR PHOTODYNAMIC/TI)

=> s l8 and l5
L9          44 L8 AND L5

=> d ibib 1-44

L9   ANSWER 1 OF 44  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1998:811260  CAPLUS
DOCUMENT NUMBER:          130:193654
TITLE:                    Spectroscopic studies of photobleaching and
                          photoproduct formation of
                          meta(tetrahydroxyphenyl)chlorin (m-THPC) used in
                          photodynamic therapy. The production of
                          singlet oxygen by m-THPC.
AUTHOR(S):                Hadjur, Christophe; Lange, Norbert; Rebstein, Julia;
                          Monnier, Philippe; van den Bergh, Hubert; Wagnieres,
                          Georges
CORPORATE SOURCE:         Inst. Environ. Eng., Swiss Fed. Inst. Technol. (EPFL),
                          Lausanne, CH-1015, Switz.
SOURCE:                   Journal of Photochemistry and Photobiology, B: Biology
                          (1998), 45(2-3), 170-178
                          CODEN: JPPBEG; ISSN: 1011-1344
PUBLISHER:                Elsevier Science S.A.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9   ANSWER 2 OF 44  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1998:708646  CAPLUS
DOCUMENT NUMBER:          130:92200
TITLE:                    Interstitial photodynamic therapy with
                          tetra(m-hydroxyphenyl)chlorin: tumor versus
                          striated muscle damage
```

AUTHOR(S): Andrejevic-Blant, Snezana; Woodtli, Alain; Wagnieres, Georges; Fontolliet, Charlotte; Van Den Bergh, Hubert; Monnier, Philippe
CORPORATE SOURCE: Department of Otolaryngology Head and Neck Surgery, CHUV Hospital, Lausanne, Switz.
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1998), 42(2), 403-412
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:679435 CAPLUS
DOCUMENT NUMBER: 130:1840
TITLE: m-THPC-mediated photodynamic therapy (PDT) does not induce resistance to chemotherapy, radiotherapy or PDT on human breast cancer cells in vitro
AUTHOR(S): Hornung, Rene; Walt, Heinrich; Crompton, Nigel E. A.; Keefe, Kristin Anne; Jentsch, Brigitte; Perewusnyk, Gloria; Haller, Urs; Kochli, Ossi R.
CORPORATE SOURCE: Research Division of Gynecology, Department of Gynecology and Obstetrics, University Hospital, Zurich, CH-8091, Switz.
SOURCE: Photochemistry and Photobiology (1998), 68(4), 569-574
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:616780 CAPLUS
DOCUMENT NUMBER: 130:22283
TITLE: Photodynamic ablation of early cancers of the stomach by means of mTHPC and laser irradiation: preliminary clinical experience
AUTHOR(S): Ell, C.; Gossner, L.; May, A.; Schneider, H. T.; Hahn, E. G.; Stolte, M.; Sroka, R.
CORPORATE SOURCE: Department of Medicine II, HSK, Wiesbaden, Germany
SOURCE: Gut (1998), 43(3), 345-349
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:567989 CAPLUS
DOCUMENT NUMBER: 129:312901
TITLE: Enhancement of tumor response to photodynamic therapy by adjuvant mycobacterium cell-wall treatment
AUTHOR(S): Korbelik, Mladen; Cecic, Ivana
CORPORATE SOURCE: Cancer Imaging Dep., British Columbia Cancer Agency, Vancouver, BC, V5Z 1L3, Can.
SOURCE: Journal of Photochemistry and Photobiology, B: Biology (1998), 44(2), 151-158
CODEN: JPPBEG; ISSN: 1011-1344

PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:522666 CAPLUS
DOCUMENT NUMBER: 129:272382
TITLE: Photodynamic therapy for gastrointestinal tumors using three photosensitizers - ALA induced PPIX, Photofrin and MTHPC. A pilot study
AUTHOR(S): Mlkvy, P.; Messmann, H.; Regula, J.; Conio, M.; Pauer, M.; Millson, C. E.; MacRobert, A. J.; Bown, S. G.
CORPORATE SOURCE: Department of Gastroenterology, St. Elisabeth Oncological Institute, Bratislava, 812 50, Slovakia
SOURCE: Neoplasma (1998), 45(3), 157-161
CODEN: NEOLA4; ISSN: 0028-2685
PUBLISHER: Slovak Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:456644 CAPLUS
DOCUMENT NUMBER: 129:227546
TITLE: mTHPC-mediated-photodynamic detection for fluorescence guided resection of brain tumors
AUTHOR(S): Kostron, Herwig; Zimmermann, Andreas; Obwegeser, Alois
CORPORATE SOURCE: Dept. of Neurosurgery, University of Innsbruck, Innsbruck, A-6020, Austria
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1998), 3262(Surgical-Assist Systems), 259-264
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:383622 CAPLUS
DOCUMENT NUMBER: 129:156538
TITLE: Effect of antioxidants on PDT treatment of cultured tumor cells
AUTHOR(S): Melnikova, V.; Bezdetnaya, L.; Belitchenko, I.; Potapenko, A.; Merlin, J. L.; Guillemina, F.
CORPORATE SOURCE: Unite de Recherche en Therapie Photodynamique, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, 54511, Fr.
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1998), 3247(Optical Methods for Tumor Treatment and Detections: Mechanisms and Techniques in Photodynamic Therapy VII), 145-149
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:383610 CAPLUS

DOCUMENT NUMBER: 129:106022
TITLE: Experimental and clinical results of mTHPC (Foscan)-mediated photodynamic therapy for malignant brain tumors
AUTHOR(S): Kostron, Herwig; Obwegeser, Alois; Jakober, Rosanna; Zimmermann, Andreas; Rueck, Angelika
CORPORATE SOURCE: University Innsbruck, Innsbruck, A-6020, Austria
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1998), 3247(Optical Methods for Tumor Treatment and Detections: Mechanisms and Techniques in Photodynamic Therapy VII), 40-45
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:267942 CAPLUS
DOCUMENT NUMBER: 129:25124
TITLE: Photodynamic therapy as a tool for suppressing the hematogenous dissemination of tumor cells
AUTHOR(S): Fischer, F.; Maier-Borst, W.; Lorenz, W.-J.
CORPORATE SOURCE: Inst. Radiol. Diagnostik Therapie, Deutsches Krebsforschungszentrum Heidelberg, Heidelberg, D-69120, Germany
SOURCE: Journal of Photochemistry and Photobiology, B: Biology (1998), 43(1), 27-33
CODEN: JPPBEG; ISSN: 1011-1344
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:238851 CAPLUS
DOCUMENT NUMBER: 128:280367
TITLE: The value of serum α-N-acetylgalactosaminidase measurement for the assessment of tumor response to radio- and photodynamic therapy
AUTHOR(S): Korbelik, M.; Naraparaju, V. R.; Yamamoto, N.
CORPORATE SOURCE: Cancer Imaging Department, British Columbia Cancer Agency, Vancouver, BC, V5Z 1L3, Can.
SOURCE: British Journal of Cancer (1998), 77(6), 1009-1014
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:101677 CAPLUS
DOCUMENT NUMBER: 128:241309
TITLE: Enhanced photodynamic effects using fractionated laser light
AUTHOR(S): Muller, Simone; Walt, Heinrich; Dobler-Girdziunaite, Diana; Fiedler, Dagmar; Haller, Urs
CORPORATE SOURCE: Switz.
SOURCE: Journal of Photochemistry and Photobiology, B: Biology (1998), 42(1), 67-70

CODEN: JPPBEG; ISSN: 1011-1344
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:722660 CAPLUS
DOCUMENT NUMBER: 128:20116
TITLE: Photodynamic therapy of early squamous cell carcinoma with tetra(m-hydroxyphenyl)chlorin: optimal drug-light interval
AUTHOR(S): Andrejevic-Blant, S.; Hadjur, Ch; Ballini, J. -P.; Wagnieres, G.; Fontolliet, Ch; Van Den Bergh, H.; Monnier, Ph
CORPORATE SOURCE: Department of Otolaryngology, Head and Neck Surgery-CHUV Hospital, Lausanne, CH-1011, Switz.
SOURCE: British Journal of Cancer (1997), 76(8), 1021-1028
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:693297 CAPLUS
DOCUMENT NUMBER: 128:11503
TITLE: Photodynamic therapy using mTHPC for malignant disease in the oral cavity
AUTHOR(S): Fan, Kathleen F.M.; Hopper, Colin; Speight, Paul M.; Buonaccorsi, Giovanni A.; Bown, Stephen G.
CORPORATE SOURCE: National Medical Laser Centre, Department of Surgery, University College London Medical School, London, UK
SOURCE: International Journal of Cancer (1997), 73(1), 25-32
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:688057 CAPLUS
DOCUMENT NUMBER: 128:20101
TITLE: Does tumor uptake of foscan determine PDT efficacy?
AUTHOR(S): Veenhuizen, Ruth; Oppelaar, Hugo; Ruevekamp, Marjan; Schellens, Jan; Dalesio, Otilia; Stewart, Fiona
CORPORATE SOURCE: Experimental Therapy Division, Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, Neth.
SOURCE: International Journal of Cancer (1997), 73(2), 236-239
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 16 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:688045 CAPLUS
DOCUMENT NUMBER: 128:20100

TITLE: Foscan-mediated photodynamic therapy for a peritoneal-cancer model: drug distribution and efficacy studies
AUTHOR(S): Veenhuizen, Ruth B.; Ruevekamp, Marjan C.; Oppelaar, Hugo; Helmerhorst, Theo J. M.; Kenemans, Peter; Stewart, Fiona A.
CORPORATE SOURCE: Experimental Therapy Division, Netherlands Cancer Institute/Antoni van Leeuwenhock Huis, Amsterdam, Neth.
SOURCE: International Journal of Cancer (1997), 73(2), 230-235
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:642470 CAPLUS
DOCUMENT NUMBER: 127:259511
TITLE: Photodynamic therapy of a transplanted pancreatic cancer model using meta-tetrahydroxyphenylchlorin (mTHPC)
AUTHOR(S): Mlkvy, P.; Messman, H.; Macrobert, A. J.; Pauer, M.; Sams, V. R.; Davies, C. L.; Stewart, J. C. M.; Bown, S. G.
CORPORATE SOURCE: National Medical Laser Centre, The Institute of Surgical Studies, University College London Medical School, London, W1P 7LD, UK
SOURCE: British Journal of Cancer (1997), 76(6), 713-718
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:606532 CAPLUS
DOCUMENT NUMBER: 127:244910
TITLE: Intraperitoneal photodynamic therapy: comparison of red and green light distribution and toxicity
AUTHOR(S): Veenhuizen, Ruth B.; Ruevekamp, Marjan C.; Oppelaar, Hugo; Ransdorp, Brigitte; van de Vijver, Mark; Helmerhorst, Theo J. M.; Kenemans, Peter; Stewart, Fiona A.
CORPORATE SOURCE: Divisions of Experimental Therapy, Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, 1066 CX, Neth.
SOURCE: Photochemistry and Photobiology (1997), 66(3), 389-395
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:229675 CAPLUS
DOCUMENT NUMBER: 126:260955
TITLE: Clinical effect of meso-tetrahydroxyphenylchlorin based photodynamic therapy in recurrent carcinoma of the ovary: preliminary results

AUTHOR(S): Wierrani, F.; Fiedler, D.; Grin, W.; Henry, M.; Dienes, E.; Gharehbaghi, K.; Krammer, B.; Grunberger, W.
CORPORATE SOURCE: Department of Gynaecology and Obstetrics, Rudolfstiftung Hospital, Vienna, A-1030, Austria
SOURCE: British Journal of Obstetrics and Gynaecology (1997), 104(3), 376-378
CODEN: BJOGAS; ISSN: 0306-5456
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 20 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:91983 CAPLUS
DOCUMENT NUMBER: 126:141495
TITLE: In vivo photodynamic therapy with meso-tetra(m-hydroxyphenyl)chlorin (mTHPC): influence of light intensity and optimization of photodynamic efficiency
AUTHOR(S): Rezzoug, Hadjira; A'amar, Oussama; Barberi-Heyob, Muriel; Merlin, Jean-Louis; Guillemin, Francois
CORPORATE SOURCE: UNITE DE THERAPIE PHOTODYNAMIQUE, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, Fr.
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1996), 2924(Photochemotherapy: Photodynamic Therapy and Other Modalities II), 181-186
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:1098 CAPLUS
DOCUMENT NUMBER: 126:115137
TITLE: In vivo fluence rate effect in photodynamic therapy of early cancers with tetra(m-hydroxyphenyl)chlorin
AUTHOR(S): Blant, Snezana Andrejevic; Woodtli, Alain; Wagnieres, Georges; Fontolliet, Charlotte; van den Bergh, Hubert; Monnier, Philippe
CORPORATE SOURCE: Dep. Otolaryngology Head Neck Surgery, CHUV Hosp., Lausanne, Switz.
SOURCE: Photochemistry and Photobiology (1996), 64(6), 963-968
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 22 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:524718 CAPLUS
DOCUMENT NUMBER: 125:189607
TITLE: Interstitial and transurethral photodynamic therapy of the canine prostate using meso-tetra-(m-hydroxyphenyl)chlorin
AUTHOR(S): Chang, Shi-Chung; Bounaccorsi, Gio; MacRobert, Alexander; Bown, Stephen G.
CORPORATE SOURCE: Medical School, University College London, London, UK
SOURCE: International Journal of Cancer (1996), 67(4), 555-562
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 23 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:471334 CAPLUS
DOCUMENT NUMBER: 125:189514
TITLE: Distribution and photodynamic effects of meso-tetrahydroxyphenylchlorin (mTHPC) in the pancreas and adjacent tissues in the Syrian golden hamster
AUTHOR(S): Mlkvy, P.; Messmann, H.; Pauer, M.; Stewart, JCM; Millson, CE; MacRobert, AJ; Bown, SG
CORPORATE SOURCE: National Cancer Centre, Bratislava, Slovakia
SOURCE: British Journal of Cancer (1996), 73(12), 1473-1479
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 24 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:418699 CAPLUS
DOCUMENT NUMBER: 125:109053
TITLE: Cellular uptake kinetics and photodynamic activity of meso-tetrahydroxyphenylchlorin (mTHPC)
AUTHOR(S): Rezzoug, Hadjira; Merlin, Jean-Louis; Zeghari, Nadia; Lignon, Dominique; Marchal, Sophie; Ramacci, Carole; Yvroud, Edouard; Guillemin, Francois
CORPORATE SOURCE: Unite de Recherche en Therapie Photodynamique, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, 54511, Fr.
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1996), 2625(Photochemistry: Photodynamic Therapy and Other Modalities), 386-394
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 25 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:418686 CAPLUS
DOCUMENT NUMBER: 125:109044
TITLE: Optimization of photodynamic therapy with chlorins for chest malignancies
AUTHOR(S): Ris, Hans-Beat; Giger, Andreas; Hof, Vinzenz Im; Althaus, Ulrich; Altermatt, Hans Jorg
CORPORATE SOURCE: Department Thoracic and Cardiovascular Surgery, University Bern, Bern, CH-3010, Switz.
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1996), 2625(Photochemistry: Photodynamic Therapy and Other Modalities), 298-301
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 26 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:418678 CAPLUS
DOCUMENT NUMBER: 125:109037
TITLE: Interstitial photodynamic therapy of canine prostate with meso-tetra-(m-hydroxyphenyl) chlorin and 5-aminolevulinic acid: A preliminary study
AUTHOR(S): Chang, Shi-Chung; Buonaccorsi, Gio; MacRobert, Alexander J.; Bown, Stephen G.
CORPORATE SOURCE: Medical School, University College London, London, UK
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1996), 2625(Photochemistry: Photodynamic Therapy and Other Modalities), 224-231
CODEN: PSISDG; ISSN: 0277-786X

PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 27 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:274609 CAPLUS
DOCUMENT NUMBER: 124:336785
TITLE: Influence of fractionation and fluence rate in photodynamic therapy with Photofrin or mTHPC
AUTHOR(S): van Geel, I. P. J.; Oppelaar, H.; Marijnissen, J. P. A.; Stewart, F. A.
CORPORATE SOURCE: Div. Experimental Therapy, Netherlands Cancer Inst., Amsterdam, 1066 CX, Neth.
SOURCE: Radiation Research (1996), 145(5), 602-609
CODEN: RAREAE; ISSN: 0033-7587
PUBLISHER: Kluge Carden Jennings Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 28 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:267452 CAPLUS
DOCUMENT NUMBER: 125:4599
TITLE: New LED source for photodynamic therapy: preclinical study
AUTHOR(S): de Jode, M. L.; Dilkes, M. G.; Grahn, M. F.; Hart, P. B.; Raven, A.
CORPORATE SOURCE: Academic Surgical Unit, Royal London Hospital, London, UK
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1996), 2629(Biomedical Optoelectronics in Clinical Chemistry and Biotechnology), 299-305
CODEN: PSISDG; ISSN: 0277-786X
PUBLISHER: SPIE-The International Society for Optical Engineering
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 29 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:148995 CAPLUS
DOCUMENT NUMBER: 124:225242
TITLE: A comparison of functional bladder damage after intravesical photodynamic therapy with three different photosensitizers
AUTHOR(S): Post, J. G.; te Poele, J. A. M.; Schuitmaker, J. J.; Stewart, F. A.
CORPORATE SOURCE: Division of Experimental Therapy, Netherlands Cancer Inst., Amsterdam, Neth.
SOURCE: Photochemistry and Photobiology (1996), 63(3), 314-21
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 30 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:111087 CAPLUS
DOCUMENT NUMBER: 124:197127
TITLE: Optical instrumentation suitable for a real time dosimetry during photodynamic therapy
AUTHOR(S): Guillemin, F.; A'Amar, O.; Rezzoug, H.; Lignon, D.; Jaffry, F.; Abdulnour, C.; Mueller, L.; Yvroud, E.; Merlin, JL.; et al.
CORPORATE SOURCE: Unite de Therapie Photodynamique, Centre Alexis Vautrin, Vandceuvre, 54511, Fr.
SOURCE: Proceedings of SPIE-The International Society for

Optical Engineering (1995), 2627, 92-9
CODEN: PSISDG; ISSN: 0277-786X
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 31 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:882041 CAPLUS
DOCUMENT NUMBER: 123:333848
TITLE: Assessment of effect of photosensitizers on cytotoxicity of photodynamic therapy in human breast cancer cell cultures
AUTHOR(S): Koechli, O. R.; Schaer, G. N.; Schenk, V.; Haller, U.; Walt, H.
CORPORATE SOURCE: Department of Obstetrics & Gynecology, University of Zurich, Zurich, CH-8091, Switz.
SOURCE: Archives of Gynecology and Obstetrics (1995), 256(4), 167-76
CODEN: AGOBEJ; ISSN: 0932-0067
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 32 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:848982 CAPLUS
DOCUMENT NUMBER: 123:309591
TITLE: Physico-chemical modeling of the role of free radicals in photodynamic therapy. III. Interactions of stable free radicals with excited photosensitizers studied by kinetic ESR spectroscopy
AUTHOR(S): Kriska, Tamas; Korecz, Laszlo; Nemes, Istvan; Gal, Dezso
CORPORATE SOURCE: Cent. Res. Inst. Chem., Hung. Acad. Sci., Budapest, H-1525, Hung.
SOURCE: Biochemical and Biophysical Research Communications (1995), 215(1), 192-8
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 33 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:750174 CAPLUS
DOCUMENT NUMBER: 123:192541
TITLE: Mechanisms for optimizing photodynamic therapy: second-generation photosensitizers in combination with mitomycin C
AUTHOR(S): van Geel, I. P. J.; Oppelaar, H.; Oussoren, Y. G.; Schuitmaker, J. J.; Stewart, F. A.
CORPORATE SOURCE: Dep. of Ophthalmology, State University of Leiden, Leiden, Neth.
SOURCE: British Journal of Cancer (1995), 72(2), 344-50
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 34 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:631847 CAPLUS
DOCUMENT NUMBER: 123:51260
TITLE: Uptake, localization, and photodynamic effect of meso-tetra(hydroxyphenyl)porphine and its corresponding chlorin in normal and tumor tissues of mice bearing mammary carcinoma
AUTHOR(S): Peng, Qian; Moan, Johan; Ma, Li-Wei; Nesland, Jahn M.

CORPORATE SOURCE: Inst. Cancer Research, Norwegian Radium Hospital, Oslo, 0310, Norway
SOURCE: Cancer Research (1995), 55(12), 2620-6
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 35 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:583710 CAPLUS
DOCUMENT NUMBER: 123:106655
TITLE: Distribution and photodynamic effect of meta-tetrahydroxyphenylchlorin (mTHPC) in the pancreas and adjacent tissues in the Syrian golden hamsters.
AUTHOR(S): Mlkvy, P.; Messmann, H.; Stewart, J. C.; Pauer, M.; Millson, C. E.; MacRobert, A. J.; Bown, S. G.
CORPORATE SOURCE: Rayne Institute, University College London, UK
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1995), 2371, 268-73
CODEN: PSISDG; ISSN: 0277-786X
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 36 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:583691 CAPLUS
DOCUMENT NUMBER: 123:78595
TITLE: Evaluation with mTHPC of "early" squamous cell carcinomas of the cheek pouch mucosa of golden Syrian hamsters as a model for clinical PDT of "early" cancers in the upper aerodigestive tract, the esophagus and the tracheobronchial tree
AUTHOR(S): Glanzmann, Thomas; Theumann, Jean-Francois; Forrer, Martin; Braichotte, Daniel; Wagnieres, Georges; Bergh, Hubert van den
CORPORATE SOURCE: Swiss Federal Institute Technology (EPFL), Lausanne, 1015, Switz.
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1995), 2371, 51-8
CODEN: PSISDG; ISSN: 0277-786X
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 37 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:555421 CAPLUS
DOCUMENT NUMBER: 123:4734
TITLE: Correlation between meta(tetrahydroxyphenyl)chlorin (m-THPC) biodistribution and photodynamic effects in mice
AUTHOR(S): Morlet, Laurent; Vonarx-Coinsmann, Veronique; Lenz, Peter; Foultier, Marie-Therese; Xavier de Brito, Leonor; Stewart, Charles; Patrice, Thierry
CORPORATE SOURCE: Physiologie, Photobiologie des Cancers, 6eme Etage, Faculte de Pharmacie, Nantes, F-44035, Fr.
SOURCE: Journal of Photochemistry and Photobiology, B: Biology (1995), 28(1), 25-32
CODEN: JPPBEG; ISSN: 1011-1344
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 38 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:486089 CAPLUS
DOCUMENT NUMBER: 122:234384
TITLE: Distribution of temoporfin, a new photosensitizer for

the photodynamic therapy of cancer
, in a murine tumor model
AUTHOR(S): Whelpton, Robin; Michael-Titus, Adina T.; Basra, Sukhbinder S.; Grahn, Michael
CORPORATE SOURCE: Dep. Pharmacology, Univ. London, London, E1 4NS, UK
SOURCE: Photochemistry and Photobiology (1995), 61(4), 397-401
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 39 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:481425 CAPLUS
DOCUMENT NUMBER: 122:259976
TITLE: An ultrastructural evaluation of CaD2 mouse mammary carcinoma after photodynamic therapy with meso-tetra(hydroxyphenyl)porphyrin (m-THPP) or its corresponding chlorin (m-THPC)
AUTHOR(S): Peng, Qian; Moan, Johan; Nesland, Jahn M.
CORPORATE SOURCE: Institute Cancer Research, Norwegian Radium Hospital, Montebello, 0310, Norway
SOURCE: Proceedings of SPIE-The International Society for Optical Engineering (1994), 2329, 280-90
CODEN: PSISDG; ISSN: 0277-786X
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 40 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:460317 CAPLUS
DOCUMENT NUMBER: 122:285638
TITLE: Photosensitizing efficacy of MTHPC-PDT compared to Photofrin-PDT in the RIF1 mouse tumor and normal skin
AUTHOR(S): Geel, Ingrid P. J. Van; Oppelaar, Hugo; Oussoren, Yvonne G.; Valk, Martin A. Van Der; Stewart, Fiona A.
CORPORATE SOURCE: Division Experimental Therapy, Netherlands Cancer Institute/Antoni van Leeuwenhoekhuis, Amsterdam, 1066 CX, Neth.
SOURCE: International Journal of Cancer (1995), 60(3), 388-94
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 41 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:341386 CAPLUS
DOCUMENT NUMBER: 122:127673
TITLE: Intraperitoneal photodynamic therapy in the rat: comparison of toxicity profiles for Photofrin and mTHPC
AUTHOR(S): Veenhuizen, Ruth B.; Ruevekamp-Helmers, Marjan C.; Helmerhorst, Theo J.M.; Kenemans, Peter; Mooi, Wolter J.; Marijnissen, Johannes P.A.; Stewart, Fiona A.
CORPORATE SOURCE: Division of Experimental Therapy, Netherlands Cancer Institute, Amsterdam, 1066 CX, Neth.
SOURCE: International Journal of Cancer (1994), 59(6), 830-6
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

L9 ANSWER 42 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:157672 CAPLUS
DOCUMENT NUMBER: 120:157672
TITLE: Photodynamic therapy with m-tetrahydroxyphenylchlorin in vivo: Optimization of

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                        the therapeutic index
AUTHOR(S):              Ris, Hans Beat; Altermatt, Hans J.; Stewart, Charles
                        M.; Schaffner, Thomas; Wang, Qiang; Lim, Chang K.;
                        Bonnett, Raymond; Althaus, Ulrich
CORPORATE SOURCE:       Dep. Thorac. Cardiovasc. Surge., Univ. Bern, Switz.
SOURCE:                 International Journal of Cancer (1993), 55(2), 245-9
                        CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE:          Journal
LANGUAGE:               English

L9   ANSWER 43 OF 44  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:       1994:100601  CAPLUS
DOCUMENT NUMBER:        120:100601
TITLE:                  Dynamic capillaroscopy: a minimally invasive technique
                        for assessing photodynamic effects in vivo
AUTHOR(S):              Menezes da Silva, Fernando A.; Newman, E. Luke
CORPORATE SOURCE:       Dep. Surgery, Univ. Dundee, Dundee, DD1 9SY, UK
SOURCE:                 Photochemistry and Photobiology (1993), 58(6), 884-9
                        CODEN: PHCBAP; ISSN: 0031-8655
DOCUMENT TYPE:          Journal
LANGUAGE:               English

L9   ANSWER 44 OF 44  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:       1993:142642  CAPLUS
DOCUMENT NUMBER:        118:142642
TITLE:                  Effect of drug-light interval on photodynamic
                        therapy with meta-tetrahydroxyphenylchlorin in
                        malignant mesothelioma
AUTHOR(S):              Ris, Hans Beat; Altermatt, Hans Joerg; Nachbur,
                        Bernhard; Stewart, J. Charles M.; Wang, Qiang; Lim,
                        Chang Kee; Bonnett, Raymond; Althaus, Ulrich
CORPORATE SOURCE:       Dep. Thoracic Cardiovasc. Surg., Univ. Bern, Bern,
                        Switz.
SOURCE:                 International Journal of Cancer (1993), 53(1), 141-6
                        CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE:          Journal
LANGUAGE:               English


=> d his

     (FILE 'HOME' ENTERED AT 09:52:24 ON 15 AUG 2006)

     FILE 'CAPLUS' ENTERED AT 09:52:32 ON 15 AUG 2006
L1           281 S 122341-38-2/RN
L2            91 S L1 NOT PY>1998
L3            71 S L2 AND (CANCER? OR TUMOR? OR NEOPLAS?)
L4         14296 S PDT OR PHOTODYNAMIC
L5            70 S L4 AND L3
L6        468285 S ANTIBOD?
L7             0 S L6 AND L5
L8          5339 S L4/TI
L9            44 S L8 AND L5

=> s l1/pn
FIELD CODES CANNOT BE CHANGED HERE
You may have tried to apply a field code to a term that already has a
field code.  You can only add a field code to a term that has no field
code appended to it.

=> s l2/pn
QUALIFICATION NOT VALID FOR NUMERIC DATA 'PY/PN'
Numeric data cannot be field qualified.
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=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	75.29	75.50

STN INTERNATIONAL LOGOFF AT 09:57:09 ON 15 AUG 2006